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ARCHIVES OF SURGERY

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PILONIDAL SINUS

AN EXPLANATION OF ITS EMBRYOLOGIC DEVELOPMENT

MIMS GAGE, M.D.

NEW ORLEANS

The term "pilonidal," derived from the Latin *pilus,* meaning hair, and *nidus,* meaning nest, was first applied to sinuses in the sacral region by Hodges [1] in 1880. However, the lesion was in all probability first described by J. W. Warren [1] in 1867. Since the first description of the lesion many terms have been suggested, such as "coccygeal, sacrococcygeal or sacral sinus, dimple or fistula"; "postanal dimple, fistula or fissure"; "posterior umbilicus"; "postsacral or sequestration dermoid." From clinical usage the term "pilonidal sinus" has supplanted practically all of the other terms. At present the term "pilonidal cyst" or "pilonidal sinus" should be limited to those cysts or sinuses having their origin from the medullary canal, which should not be confused with the simple type of sacral dimple.

The etiology of this interesting anomaly has been most intriguing to the majority of writers describing the sinus, as attested by the numerous and, in some instances, fanciful theories regarding its formation. However, most of the authors agree that this clinical entity is a congenital malformation.

Warren, probably the first to offer a theory concerning the formation of a pilonidal cyst, suggested in 1867 that it is due to a change in growth of the hair follicles in the sacral region. Hodges, in 1880, thought it to be due to invaginations of hairs in the postnatal fold. Mallory,[2] Tourneaux [3] and Oehlecker [4] demonstrated vestiges from this canal that formed cysts and sinuses in the sacral region in the fetus. According to Kuhn,[5] such findings were residua of spina bifida, whereas Tait [6] thought they were residua of the caudal appendage. Féré [5] considered the failure of the two halves of the body to unite responsible

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1. Quoted by Gleen, Frank: Pilonidal Sinus, New England J. Med. **207:** 544, 1932.
2. Mallory, F. B.: Am. J. M. Sc. **103:**269, 1892.
3. Tourneaux and Hermann, quoted by Keibel and Mall.[10]
4. Oehlecker, F.: Sacral Abscesses in Congenital Skin Displacements, Deutsche Ztschr. f. Chir. **197:**262, 1926.
5. Quoted by Couraud.[1]
6. Quoted by Weeder, S. D.: Pilonidal Cyst, Ann. Surg. **98:**385, 1933.

for their formation. Welen Stadt [1] stated that "the spinal cord was the last portion to lose its connection with the skin. Therefore, the sacrum in closing its dorsal aspect pinches off the skin, leaving a fibrous cord which causes the skin to retract as the parts grow out, thus forming a dimple." Mummery [1] believed that the sinus is only an exaggeration of the postnatal dimple and that it is a sequestration dermoid due to inclusion of skin. Bevan [7] suggested that the sinus develops congenitally from a bur of epithelium which has been turned under the integument, and Bookman [6] believed that the sinus occurs as a result of the breaking down of sacrococcygeal cysts. In 1924 Stone [8] stated that "the sinus developed from a special downgrowth of the epithelium and not from the medullary canal." He was unable at that time to name the etiologic factor responsible for this downgrowth of true skin. However, in 1931, he explained this special downgrowth of true skin by comparing the pilonidal sinus found in man, in its development and formation, to the preen gland that occurs in a great many species of birds. Wharton [9] agreed with Stone and considered the analogy to the preen gland to be an excellent explanation of the development of the pilonidal sinus. Other interesting explanations have been given. However, by reviewing a few of the different theories of the origin of pilonidal cysts, one can see how incomplete the knowledge of their formation and development is at the present time. I believe this wide diversity of opinions regarding the origin, formation and development of pilonidal cysts and sinuses to be responsible for the high incidence of recurrence following attempts at surgical removal. I am convinced that the only way one can satisfactorily determine the origin of pilonidal cysts and draw definite conclusions is by studying the embryologic development of the caudal end of the embryo with special reference to the development of the integument, its appendages and the nervous system. This should be correlated with a clinical study of cases of pilonidal sinus as well as with pathologic and histologic studies, with differential staining of numerous sections, removed from different areas of tissue obtained at operation. The object of this paper is to present evidence (which in the author's opinion is conclusive) deduced by these methods of study to show that the pilonidal sinus results from an anomalous development of the medullary canal, and that the coccygeal dimple results from disturbances in the development of the coccygeal ligament and is not connected with the medullary canal.

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7. Bevan, A. D., quoted by Anderson, J. K.: Diagnosis and Treatment of Pilonidal Sinus, Minnesota Med. **14**:421, 1931.

8. Stone, Harvey B.: Pilonidal Sinus, Ann. Surg. **79**:410, 1924; **94**:317, 1931.

9. Wharton, D. J.: Pilonidal Cyst, U. S. Nav. M. Bull. **30**:350, 1932.

EMBRYOLOGY OF CAUDAL END OF EMBRYO

The embryologic development of the caudal end of the embryo will now be reviewed, with special attention to the ectoderm, its derivatives and the mesoderm—to the latter only as it applies to the formation of the sacrum, coccyx and coccygeal ligament. I believe that the entire solution of this interesting problem is dependent on an understanding of the developmental anomalies occurring in these germ layers in the caudal anlage of the embryo.

After the formation of the ectoderm and entoderm, the indentation, or primitive streak, occurs. Soon two folds appear on each side of the streak. These ridges are known as the medullary folds and give rise to the medullary groove. While the medullary folds increase in height the medullary groove increases correspondingly in depth. When the medullary folds increase in height they incline toward each other, so that their edges finally come in contact and later fuse. By this process the medullary groove becomes converted into the medullary canal. The mesoderm begins to grow in from the sides between the ectoderm and the entoderm to form the supportive structure of the newly formed neural canal. This medullary canal later becomes the central nervous system by a process of evolution of the primitive cells of the walls of the canal, the canal proper, persisting as the central canal of the spinal cord, widening out in the cephalic end to form the ventricles of the brain. The layer of ectoderm that forms the roof remains attached to the medullary canal by a mass of cells. On the dorsal surface, this mass of cells represents the neural crest. However, as development proceeds the ectoderm is entirely separated from the neural crest, which continues to develop lateral to the medullary canal, giving rise to the spinal ganglions and sympathetic nervous system. (Keibel and Mall,[10] Hardesty [11] and McMurrich [12]). The closure of the medullary groove starts near the future cervical region and spreads in both directions. Therefore, the caudal end closes later than the cephalic. At about this period of development of the embryo special consideration of the caudal end of the medullary canal is advisable. This part of the medullary canal exhibits departures from the uniform development of that part of the canal from which the spinal cord and brain develop. If one examines a sagittal series through an embryo 11 cm. long, it can be seen that the extreme tip of the cord lying in the tail anlage has been closed off from the rest of the medullary canal to form a simple

10. Keibel, F., and Mall, F. P.: Human Embryology, Philadelphia, J. P. Lippincott Company, 1912, vol. 2, p. 57.

11. Hardesty, in Morris: Human Anatomy, edited by C. M. Jackson, ed. 5, Philadelphia, P. Blakiston's Son & Company, 1914, pt. 3.

12. McMurrich, J. P.: The Development of the Human Body, ed. 4, Philadelphia, P. Blakiston's Son & Company, 1914.

epithelial sac. The lumen of the cord above this point becomes obliterated, and there results a slender strand of nervous tissue which later becomes the filum terminale. The epithelial sac becomes the *"vestiges medullaire coccygiene"* of Tourneaux and Hermann.[3] Tourneaux described the development of the sac as follows: "At the beginning of the third month the neural tube still extends to the extreme end of the vertebral column into the tail bud, and its slightly elongated tip is closely united to the deep layers of the skin." The tube may remain patent at its junction with the skin (Mallory[2]). Toward the end of the third month the spinal column, developing faster than the soft parts, draws along that part of the neural canal which is adherent to it, the extreme tip of which remains attached to the skin. As a result of the unequal growth the terminus of the coccygeal portion of the neural canal becomes bent in the form of a loop, the more deeply situated limb of which is attached to the posterior surface of the coccyx (*segment coccygien direct*), while the more superficial limb extends obliquely from a caudal and ventral position to one more dorsal and cranial (*segment coccygien reflecti*). During the course of the fourth month the more deeply situated limb atrophies and disappears, while the more superficial one continues to develop into the fifth month and gives origin to cell cords or cell masses which contain cavities lined either with prismatic or with pavement epithelium. These structures from the sixth month on suffer a progressive atrophy, but it is possible to recognize traces of them up to the time of birth.

According to Mallory,[2] who has examined a number of fetuses from 3 to 4 months old, there is frequently found over the coccyx a canal lined by epithelium. In some instances the canal is connected with the skin; in other instances it is separated from it. This canal may be close to the skin without communicating with it, or it may be situated near the periosteum on the dorsal surface of the coccyx.

According to Oehlecker,[4] one can distinguish in the 12 mm. embryo a vertebral and a nonvertebral tissue, the nonvertebral portion being known as the caudal filament. This filament is a prolongation of the connective tissue of the caudal vertebrae. The caudal vertebrae now begin to grow rapidly, and the overlying skin, being unable to keep pace with the downward progress of the caudal vertebrae, is displaced posteriorly and upward, as is also the tip of the caudal filament or ligament. By the fourth or fifth month the skin which originally covered the tip of the coccyx is drawn upward and now occupies a position over the third or fourth caudal vertebra. At the site of attachment of the caudal ligament to the skin there is a thin, hairless, vascular area which Oehlecker has named the "sacral bald spot" of the embryo. The caudal ligament attached to the skin exerts a certain pull on the skin at the point of attachment, producing a depression of the skin. This

depression is known as the coccygeal dimple. Oehlecker also demonstrated that the caudal vestiges of the medullary canal form epithelial-lined spaces and sinuses located over the upper part of the coccyx or lower part of the sacrum. In this observation he is in agreement with Mallory,[2] Tourneaux and Hermann [3] and Keibel and Mall.[10] Therefore, one can state from the observations of these authors that the formation of these epithelial-lined spaces situated over the sacro-coccygeal region, which may or may not have a communication with the skin, has a definite embryologic basis.

Another observation that has been proved beyond doubt is that these cystic cavities and sinuses in the embryo, as well as the same cysts and sinuses in the adult, are lined with epithelium of the pavement or stratified type. Therefore, a review of the development of the skin and its appendages will explain some of the histologic peculiarities found associated with the epithelial lining of the cysts and sinuses removed by operation from children and adults. The following description is from Maximow.[13]

> During the first two months of embryonic life the epidermis is represented by two layers of cells, the external and internal. The internal layer which lies on the mesenchyme consists of cuboidal or cylindrical cells which multiply rapidly. The peripheral layer, the so-called peridermis, consists of thin flat cells which do not multiply independently, but which are constantly formed anew from the elements of the deep layer.
>
> Beginning with the third month, the peripheral cells become cornified in certain places and are transformed into large, thin, thorny scales, without the participation of keratohyalin or eleidin; they are gradually desquamated. The epidermis at this time becomes three-layered and still later stratified. Between the peridermis and the basal layer the interstitial layer appears, at first consisting of separate cells, then of one continuous row of flattened elements, and still later of polyhedral cells which increase in number, and are flattened towards the surface. These cells are connected with one another by intercellular bridges, and are penetrated by tonofibrils located in the ectoplasm.
>
> The first appendage of the skin and probably the most primitive of all the appendages is the hair follicle and hair shaft. In man the hair first appears at the end of the second month in the eyebrows, and on the chin and upper lip. Hair always develops in the same manner. At first in the deep layer of the epidermis a group of closely adjoining cylindrical dividing cells appear. These grow into the underlying connective tissue and produce a gradual elongating, compact, epithelial cylinder. This is the primordium of the hair follicle, the so-called "hair germ." It is rounded and slightly flattened on its end. Connective tissue condenses under the latter very early, and from it the hair papilla forms, and proceeds from below into the epithelial mass of the bulb, which at this time forms a cap for the papilla. The epithelial cells at the surface of the connective tissue papilla represent the matrix of the future hair. The axis of the bulb is not perpendicular to the surface of the skin but is oblique.

13. Maximow, A. A.: A Text-Book of Histology, edited by William Bloom, Philadelphia, W. B. Saunders Company, 1930.

The sebaceous glands develop from the formed hair shafts. The primordium of the sebaceous gland develops from the posterior part of the epithelial sheath of the hair shaft, first by proliferation of the epithelial cells with subsequent outgrowth of these cells into the surrounding connective tissue. The central cells early undergo a fatty transformation, forming the first evidence of the future sebaceous gland. These central cells desquamate and are discharged from the hair shaft on to the surface of the body of the fetus, forming the vernix caseosa.

The last appendage of the epidermis to be formed is the sweat gland, which develops independently of the hairs in the majority of places of the skin. The first primordia of the sweat glands occur during the fifth month of embryonic life, on the soles of the feet, and the palmar surfaces of the fingers. At first they are similar to the primordia of the hair follicle which develops from the same basal layer of epithelium. An epithelial shaft with terminal thickening grows into the underlying connective tissue, but unlike the hairs, the connective tissue here does not condense about the epithelium. The shaft gradually elongates, becomes cylindrical, and its lower end curls into the form of a ball. Beginning with the seventh month an irregular lumen forms in this lower portion which constitutes the secretory part; along the course of the future excretory duct another lumen develops which later enters with the secretory part. The entire apparatus of the sweat gland, secretory part and the excretory part, start their development about the fifth month and are complete about the seventh month of embryonic life.

PREDICTABLE ABNORMAL DEVELOPMENTS

From the foregoing description of the embryologic development of the caudal end of the neural canal in the fetus, one can predict that certain formations occur. Of importance in explaining these formations is a knowledge of the conversion of the caudal end of the neural canal into the filum terminale, the development of the sacral and coccygeal vertebrae, the caudal ligament, and its peculiar attachment to the skin, the development of the integument or covering of the body as well as the development of the several appendages of this integument. These formations occur with such regularity that any deviation from normal may result in the persistence of these formations which become abnormal in their growth and development. This is in conformity with the law of Rienhoff,[14] which states: "There is in the life cycle of a cell or tissue, which is differentiating or growing, a period in which the cell is very sensitive to its environment, and any injury of it at this stage will result in the abnormal growth and development of that cell or structure."

The embryologic structures or formations that can be predicted with certainty are as follows:

(*a*) In the closure of the caudal end of the neural canal, that part of the canal between the coccygeal vertebrae and the skin becomes closed off from the rest of the canal and remains a cavity, which is lined with that part of the epidermis which has been segregated to form the central

14. Rienhoff, W. F.: Congenital Arteriovenous Fistula, Bull. Johns Hopkins Hosp. **25**:271, 1924.

nervous system. This cavity or cystic space may be situated near the skin with an opening or openings onto the surface of the skin, or may be near the periosteum of the sacrococcygeal union without any connection with or opening onto the skin. This blind pouch of the neural canal will, by cohesion of its walls and subsequent obliteration, disappear about the sixth month. However, this structure may persist into postnatal life, as has been demonstrated by Mallory,[2] Tourneaux, Keibel and Mall[10] and Oehlecker.[4] That part of the neural canal proximal to this closed-off end becomes obliterated and forms a solid cord which is known as the filum terminale.

This canal, which is lined by epidermal tissue, has no function as regards the development of nervous tissue; therefore, it may fail to obliterate and remain patent in part or in whole. If this condition should exist, a connection of this canal with the cystic cavity mentioned in the foregoing paragraph would be present which would consist of an epithelial-lined canal extending for various depths toward the conus of the spinal cord from an opening on the cutaneous surface in the sacrococcygeal region. The depth to which this patent canal may extend varies. It may extend to the hiatus of the sacral canal, may penetrate this covering of the hiatus and extend into the sacral canal from just beneath the sacral hiatus up to the dura, or it may be continuous with the spinal cord. That such an anomaly does exist has been demonstrated in cases reported in the literature and also in one of the cases reported in this paper.

That similar conditions exist in the embryo and persist into postnatal life is well known. Analogous changes occur in the formation, development and descent of the testicle with its tunica vaginalis. If that part of the peritoneum forming the tunica vaginalis fails to obliterate, there remains a patent canal extending from the peritoneal cavity to the base of the testicle. This formation explains the preformed sac in congenital indirect inguinal hernia. If the canal is closed only at the internal ring, a large hydrocele develops, because the cells lining the unobliterated tunica are secretory. When the tunica is obliterated partially, from the testicle toward the internal ring, or if it is patent for a short distance along the cord, various types of hydrocele of the cord occur. Where similar epithelial-lined canals fail to obliterate normally they may remain patent in part or in whole. This has been demonstrated embryologically and clinically in various organs and tissues of the body.

(*b*) A complete understanding of the epidermis, its formations and developmental peculiarities in the formation of the nervous system and the skin appendages is important: The epidermis by a process of infolding forms the neural canal; the individual characteristics of the epidermal cell are then lost by a process of cellular division and differentiation, resulting in the formation of the nerve tissue that will form the

future brain and cord. In the caudal end of the neural canal a different process takes place. As the caudal end of the canal obliterates and forms a cord of tissue recognized postnatally as the filum terminale, the epidermis that forms this canal takes no part in the formation of the true spinal cord. Therefore, if nerve tissue should develop from this part of the canal it would be rudimentary and more or less embryonic, and no definite nervous structure would be formed.

The neural canal is completely formed before the appearance of the most primitive of the appendages of the epidermis, i. e., hair shafts. The sebaceous glands appear next at a time which corresponds to the second or third month of embryonic life, after the fetus is fully formed. The sweat glands do not appear until the fifth month and are completely formed about the seventh. Therefore, the entire nervous system has differentiated into its component parts and is completely formed, the neural canal is obliterated and the filum terminale has anchored the spinal cord to the first segment of the coccyx or to the dorsal surface of the coccygeal vertebrae before all of the appendages of the skin occur.

If there has been a failure of the blind pouch or cystic cavity to obliterate in its entirety there remains a cavity lined by epidermis that was intended to form the caudal part of the neural canal. Therefore, it has lost its totipotentiality of the true epidermis, and if appendages develop at all they will be most rudimentary. As no appendage makes its appearance before the second month, and as the neural canal has been closed off before this time, the epidermal lining of this cystic cavity in all probability retains the power to form the most primitive appendage, the hair follicle and hair shaft. This same condition would exist if the neural canal failed to obliterate distal to the sacrococcygeal union. One would expect to find a canal lined with epidermis containing no appendages with the exception of hair and hair follicles (fig. 1). If, however, the neural canal failed to obliterate and extended into the sacral canal, was attached to the dura or was continuous with the spinal cord, the power to form appendages would in all probability be completely lost, and there would be only an undeveloped epidermis.

Therefore, the nearer to the spinal cord this part of the caudal canal remains unobliterated, the more closely will it be associated with the formation of nerve tissue, and in some instances it should be possible to find rudimentary or embryonic nerve tissue along the patent canal.

All of these findings I have been able to demonstrate microscopically in a large number of sections of surgically removed pilonidal sinuses. By differential staining in one instance in which the neural canal was patent up to the dura, I have demonstrated embryonic nerve tissue just beneath the epithelial lining of the canal (figs. 2 and 3). The epidermis

lining the canal did not reveal a single appendage of the true skin, which was anticipated. The finding of this nerve tissue was confirmed by staining the section with Masson's stain. The character of this tissue was determined by staining the tissue section with phosphotungstic acid hematoxylin. The latter stain demonstrated the fine fibrils running in the mass of young nerve cells to be neuroglia fibrils. The demonstration of the presence of embryonic nerve tissue along that part of the unobliterated neural tube located in the sacral canal has a

Fig. 1.—Photomicrograph through the center of the sinus showing the sinus tract lined by squamous epithelium. The epithelium has been desquamated and eroded as shown in the lower left corner. There are no sebaceous or sweat glands in this section. Hair shafts can be seen in the lumen of the sinus.

most important bearing on the origin of the pilonidal sinus from the neural canal as well as the development of gliomas in the sacrococcygeal region.

(*c*) The last caudal vertebra is attached to the skin by a prolongation of the mesoderm from the tip of the last coccygeal vertebra to the epidermis. Because the vertebrae grow more rapidly than the overlying

skin the caudal ligament becomes reflected dorsalward, and at the third or fourth month the skin which is attached to the caudal ligament lies over the third or fourth caudal vertebra. According to Oehlecker, the site of attachment of the caudal ligament to the skin marks an area in the skin ("sacral bald spot") that is devoid of hair and is vascular. If the development of the caudal ligament does not proceed normally with the upward progress of the skin, owing to the rapid downward development of the caudal vertebrae, the ligament remains short and the

Fig. 2.—Photomicrograph of section taken from the sinus tract within the sacral canal. This shows the edge of the sinus tract lined by squamous epithelium. There are no hair shafts, hair follicles, sebaceous or sweat glands. The arrows point to an area of embryonic glial tissue, which is just beneath the epithelial lining of the tract.

overlying skin is retracted toward the coccyx by the pull of this ligament, which produces a depression or dimple. The ligament finally becomes a part of the periosteum over the coccygeal vertebrae, and the skin becomes fixed to the deep connective tissue by this attachment. As the buttocks grow outward in their normal process of development there remains a depression in the overlying skin, this depression being known

as the sacrococcygeal dimple. If this dimple persists into adult life, the lower end of the dimple will be pulled in deeper than the more cephalic part. This increasing pull produced mainly by the skin fixation and increasing bulk of the nates, will change the dimple into a funnel-shape sinus with the lowermost part pointing toward the anus. There may develop an overlying bridge of skin which can produce a condition similar to the true type of patent neural canal.

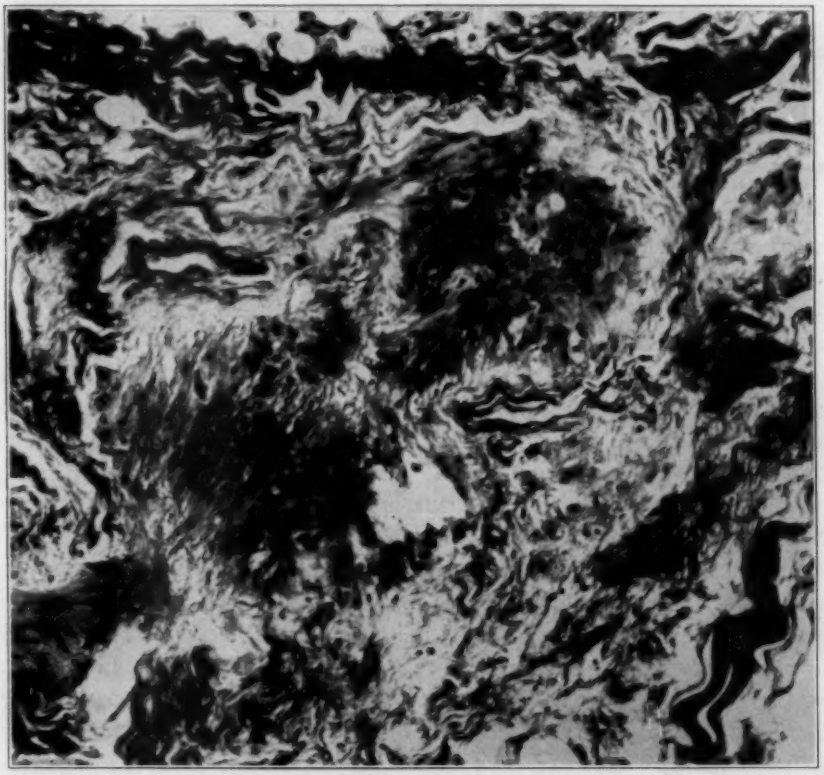

Fig. 3.—Photomicrograph, low power, showing area of embryonic nerve tissue depicted in figure 2, stained by Masson's differential stain.

That this developmental defect occurs as described in the foregoing paragraph has been demonstrated both embryologically and postnatally. The sacrococcygeal dimple has been demonstrated in both children and adults by many investigators as well as in two cases which are now reported:

In case 1, that of a child, this developmental defect was represented by a coccygeal dimple about 0.5 cm. deep. That it was due to the pull of the coccygeal ligament was demonstrated at operation, because section of the connective tissue fibers beneath the dimple allowed the dimple immediately to lose its depression and smooth out level with the normal contour of the surrounding skin.

In case 2, that of an adult, there was a sinus at the lower end of the dimple. Surgical removal revealed in the gross specimen a band of connective tissue fibers that were attached to the under surface of the epidermis, exerting a downward pull on the skin, which was responsible for the dimple and for the sinus formation. Study of sections from both failed to reveal hair shafts or follicles.

These two observations corroborate the findings of Oehlecker, who demonstrated the sacrococcygeal dimple in the embryo, and termed it the "sacral bald spot."

I believe that conclusive evidence has been presented to show that the sacrococcygeal dimple and the pilonidal cyst develop from two separate and distinct embryologic developmental defects. The sacrococcygeal dimple results from anomalous development of the caudal ligament and its attachment to the skin. This developmental anomaly can be traced from the embryo to the postnatal adult stage, and histologic examination of tissue removed from this defect found clinically in the adult corresponds exactly to the histology of the sacral dimple found in the embryo. That the various types of pilonidal cysts are results of embryologic developmental defects occurring in the caudal end of the neural canal I believe to be an established fact.

The clinical types described in the literature could hardly occur if there were not a preexisting sinus or canal from which the postnatal sinuses could develop, and this preexisting sinus or canal is represented in the embryo by the neural canal. Conclusive evidence has been found in the cases of pilonidal cyst occurring in adults, in which the tract of the sinus may extend from an opening in the skin of the sacral area to the sacrococcygeal membrane or into the sacral canal for varying distances. It may extend to the dura or may even be continuous with the spinal cord. Normal epidermal appendages, except hair follicles, could hardly develop from cells that have been differentiated to form another organ before the embryologic development of these appendages begins. This has been substantiated by a study of the specimens removed at operation. There are no appendages except hair shafts developing from the epithelial lining of the sinus tract. The epithelial lining of the sinus that approaches the spinal cord produces no appendages. The finding of embryonic neuroglia cells and fibrils associated with the sinus tract in the sacral canal could not be explained unless they had developed from the embryonic neural canal. Therefore, I believe that the various clinical types of pilonidal sinus have their origin from the caudal end of the neural canal.

I have divided the clinical cases of pilonidal cysts and sinuses into four groups, in order to facilitate the diagnosis of such conditions and as an aid in their treatment. I believe that this grouping as regards treatment will have a great tendency to prevent recurrences, which ordinarily vary between 30 and 50 per cent.

Group 1. In this group are included all the cases of sacrococcygeal dimple. This anomaly is the simplest both embryologically and clinically. The cyst or sinus is superficial, and the tract does not penetrate to the periosteum of the sacrum or coccyx.

Group 2. In this group are included the cases of true pilonidal sinus. The sinus usually extends for varying depths from the skin; it may be situated just beneath the skin, or it may extend down to the periosteum of the sacrum or coccyx. It may have a bulbous dilatation at either end, just beneath the skin or near the periosteum of the sacrum.

Group 3. In this group are included the cases in which the sinus extends down between the sacrum and coccyx or enters the sacral canal for varying distances, even extending to the dura at the level of the second sacral vertebra. The site of the cutaneous opening of the sinus varies in position but corresponds to the closure defects of the bony covering of the sacral vertebrae.

Group 4. In this group, the rarest of all, are the cases in which the sinus is complete and communicates with the spinal cord. Cerebrospinal fluid is discharged from the sinus in varying amounts. The amount, however, is usually very small.

ILLUSTRATIVE CASES

A few selected cases will now be presented, corresponding with the foregoing classification.

Type 1.—Case 1.—J. L., a girl, white, aged 8 years, was admitted to the hospital on June 20 and was discharged on Aug. 12, 1933. The chief complaint was of a dimple of the coccygeal region. Examination revealed a small dimple situated above the dorsal aspect of the coccyx near its junction with the sacrum. The dimple was about 0.5 cm. in diameter and extended below the surface of the skin for about 0.5 cm. No sinus was present.

Under local anesthesia, an elliptic incision revealed fibrous connective tissue bands extending from the under surface of the dimple to the coccyx. Following division of these fibers the dimple immediately disappeared and flattened out level with the surrounding skin. This observation confirms that of Oehlecker, and is definite proof that the dimple was caused by a pull of the coccygeal ligament on the skin.

The histologic examination revealed no hair follicles in the skin removed.

Case 2.—E. T., a white man aged 31 years, was admitted to the hospital on October 16 and was discharged on Nov. 3, 1933. He complained of pain over the coccyx which had been present for three months. About three weeks after the onset of pain, the patient noticed a yellowish discharge from the coccygeal area.

Examination showed a shallow sinus over the coccyx, extending toward the anus. There were two sinuses discharging pus on the right side of this dimple. The lower sinus had a small papilloma at its exit on the skin. Both sinuses communicated with the coccygeal sinus.

At operation, under gas anesthesia, the dimple with its accompanying sinuses was removed by an elliptic incision which extended down to the coccyx. The wound was closed, with drainage.

Gross examination of the specimen revealed a typical coccygeal dimple with radiating strands of connective tissue attached to the skin and extending downward to the coccyx. There was a small sinus at the inferior part of the dimple, due to the pull of these connective tissue strands.

On histologic examination, the sinus was found to be lined by epithelium without the presence of hair or hair follicles. A chronic inflammatory reaction was present.

In these cases the lesion was a coccygeal dimple produced by the pull of the coccygeal ligament on the skin.

Type 2.—Case 3.—E. V., a white man, aged 24 years, was admitted to the hospital on October 4 and discharged on Oct. 16, 1933. His chief complaint was of a discharging sinus between the buttocks. Examination revealed a discharging sinus in the area of the sacrococcygeal region. There were five sinuses in a straight line in the midline over a distance of about 3 cm. A diagnosis of pilonidal cyst was made.

At operation, the entire area containing the sinuses was removed by an elliptic incision which extended down to the periosteum of the sacrococcygeal region. The wound was closed with interrupted silkworm gut sutures, with a rubber drain at the lower angle. Except for a small area of skin, the wound healed by primary intention.

Examination of the gross specimen showed two cystic cavities about 1 cm. in diameter, connected with each other by a sinus about 0.25 cm. in diameter and about 1 cm. long. These two cysts and the connecting sinus were situated just beneath the skin and connected with it by five openings, two openings leading into the upper cyst and three into the lower cyst. These cystic cavities and the sinus did not extend more than 1 cm. below the skin surface.

Histologic examination revealed that both cystic cavities were lined by stratified squamous epithelium. Numerous hair follicles but no sebaceous or sweat glands were present. This condition corroborates the description of pilonidal cysts by Tourneaux as *"vestiges coccygiens reflecti."* This cyst presented both clinical and histologic evidence of having had its origin from the terminal portion of the medullary canal.

Case 4.—B. A., a white youth aged 17 years, was admitted to the hospital on April 5, was operated on April 6 and discharged on April 17, 1933. He complained of pain in the sacral region. Six months previously, he injured his back in the region of the sacrum. An abscess developed after the injury which soon ruptured and drained. After that he had intermittent pain in the sacral region. Examination showed two small sinuses near the sacrococcygeal joint. A probe inserted into each extended for about 2 cm. toward the sacrococcygeal hiatus. The diagnosis was pilonidal sinus.

At operation, under ether anesthesia, an elliptic incision, 10 cm. long, circumscribing the sinus area, was made. The entire mass was excised, and the sinus tract was found to extend to the periosteum, but did not involve it. The wound was closed, with drainage. The patient made an uneventful recovery.

Microscopic examination showed a chronic inflammatory reaction around the sinus tract. Hairs and hair follicles were present, but no sebaceous or sweat glands.

This case is one in which the medullary canal failed to close, resulting in the formation of a sinus that extended from an opening on the skin down to the periosteum of the sacrum.

Type 3.—Case 5.—Z. F., a woman aged 30 years, was hospitalized on April 8 and discharged on June 6, 1933. This patient was operated on two years pre-

viously for a pilonidal sinus, at which time the sinus was dissected down to the sacrococcygeal region and the coccyx removed. The wound took several weeks to heal.

On readmission to the hospital she complained of a discharging sinus in the region of the old operation. Examination revealed a scar in the sacrococcygeal region with a sinus in the scar. The patient was operated on, on June 15. The sinus was dissected with the scar tissue extending down into the sacral region. The sinus and the surrounding tissue were represented by a cordlike structure about 0.5 cm. in diameter. After careful dissection into the sacral canal, the tissue was pulled on and severed with scissors; there was an immediate gush of cerebrospinal fluid into the wound. The entire wound was packed with iodoform gauze and loosely closed with sutures.

Histologic examination of this tissue revealed a sinus tract, lined by stratified squamous epithelium, incompletely developed. There were no skin appendages, hair, sebaceous glands or sweat glands present. An important finding in the sinus tract was that of embryonic nerve tissue, which by differential staining proved to be neuroglia.

The patient recovered and the wound was completely healed at the time of her discharge from the hospital.

Type 4.—Case 6.—Moise [15] reported a case of staphylococcic meningitis secondary to a congenital sinus. The patient, a white youth aged 18 years, since birth had had a persistent sinus situated over the upper part of the sacrum. It communicated with the spinal cord, and discharged a watery fluid intermittently. At operation, by injecting methylene blue into the sinus, it was found to communicate with the spinal canal. Continuous drainage was established by resecting the sinus and performing a laminectomy. The patient recovered.

There was associated with this sinus a congenital malformation of the sacrum which Moise interpreted as spina bifida occulta.

This case represents one of the rarest types of pilonidal cysts, one in which there was complete failure of obliteration of the caudal end of the medullary canal. The sinus tract was lined by stratified squamous epithelium, but no mention was made of the presence of skin appendages.

Case 7.—Ripley and Thompson [16] reported a case of staphylococcic meningitis occurring in a child, 3½ months old, secondary to a pilonidal cyst located over the second sacral vertebra. In this case the sacral arch was deficient. The sinus led from the skin to a sac over the second sacral vertebra. The sac contained hair and sebaceous material. The base of the sac communicated with the spinal cord, an observation which was verified at autopsy. The child had a defect in the arches of the sacrum as well as a pilonidal sinus in the region of the second sacral vertebra. The sinus communicated with the spinal canal and was the portal of entry in the development of meningitis of the staphylococcic type.

The cases cited by Moise and Ripley and Thompson represent cases in group 4, in which the embryologic defect consists of failure of obliteration of the caudal end of the medullary canal.

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15. Moise, T. S.: Staphylococcus Meningitis Secondary to Congenital Sacral Sinus, Surg. Gynec. & Obst. **42**:394, 1926.

16. Ripley, W., and Thompson, D. C.: Pilonidal Sinus as Route of Infection in Case of Staphylococcus Meningitis, Am. J. Dis. Child. **36**:785 (Oct.) 1928.

INTRADIPLOIC EPIDERMOID (CHOLESTEATOMA) OF THE SKULL

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Epidermoids are relatively rare neoplasms which occur most frequently in and about the nervous system, particularly in its cranial portion. They have been called cholesteatomas, *tumeurs perlées, Perlgeschwulst* and atheroma. They may arise beneath the scalp, within the diploe, between the bone and the dura mater, beneath the arachnoid membrane, particularly about the base of the brain, or within the ventricles. It is now commonly accepted that these tumors arise from ectodermal rests—a hypothesis originally advanced by Remak [1] in 1854, although it was not universally accepted until many years later. Such embryonic rests are probably remnants of an incomplete separation of the neural from the surface ectoderm. Such epithelial anlagen when located within or near the nervous structures form the intraventricular and subarachnoid epidermoids. At other times they have been deposited between the two ectodermal structures, skin and brain, and surrounded by mesodermal tissues, thus forming the epidural, intradiploic and epicranial tumors. It is of interest to note that when such embryonal rests maintain their connection with the surface epithelium, which they seem to do most frequently in the spinal region, they form congenital dermal sinuses which may be the pathway for the entrance of infection into the meninges, producing subdural abscesses and meningitis.[2]

In this report I am primarily concerned with those epidermoids which arise within the diploe of the skull. These are rare, only thirteen having been reported in the literature, with the three reported here making a total of sixteen. In this connection it should be noted that similar tumors may arise in connection with the middle ear and the frontal sinuses which are undoubtedly closely related to the condition in the cases reported here. However, as the extensive literature dealing with them is greatly confused by the problem of the masses of infectious débris known as pseudocholesteatomas which arise in these regions,

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From the National Hospital for Nervous Diseases, Queen Square, London, England, and the Department of Surgery (Neurosurgery), the University of Chicago.

1. Remak, R.: Ein Beitrag zur Entwickelungsgeschichte der krebshaften Geschwülste, Deutsche Klin. **6**:170, 1854.

2. Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses, Brain **57**: 401, 1934.

particularly in and about the ear, these tumors will be omitted from the discussion and left in the province of the otologist and rhinologist.

Intradiploic epidermoids, though frequently large and commonly compressing the brain, are rarely productive of neurologic symptoms. The clinical and roentgenologic picture which they cause is, however, typical and hardly to be confused with any other condition. On examination one usually finds a swelling on the surface of the skull which has, in the majority of cases, been observed in some degree for many years, commonly from childhood. It is associated with a palpable defect in the skull, the edges of which are often raised, forming a bony ridge about all or part of the tumor. The mass is soft, may be fluctuant and may pulsate, depending on the intactness of the internal table of the skull. Roentgen examination reveals a defect in the bones of the skull which may or may not be regular. The margins of the defect may have a scalloped appearance, particularly well shown in King's first case.[3] The defect is caused by the tumor which arises within the diploe spreading and eroding the inner and outer tables of the skull. At operation an encapsulated cyst is found, the contents of which consist of white lamellae presenting the appearance of mother-of-pearl and a more or less extensive whitish-yellow caseous mass. The capsule is invariably thin and friable and is often separated from its bony crater and the dura mater with difficulty. For this reason Cushing[4] advised the reflection of an osteoplastic flap which completely included the bony defect in order that the tumor might first be separated from the dura mater and then removed from its bony crater intact. This is undoubtedly the procedure of choice when the outer table is only elevated and but slightly eroded whereas the inner table has been destroyed, but in cases in which the reverse is true, as in the cases reported here, it is hardly necessary. It is important, however, that the wall of the cyst, composed of a stratified squamous epithelium which is the only living, growing part of the neoplasm, be removed completely in order to prevent recurrence. Simple evacuation of the cyst will not suffice.

In addition, Sir Percy Sargent was wont to point out that even though the inner table of the skull seems intact it is almost invariably fractured or eroded over a small area. Through this defect the tumor

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3. King, J. E. J., cited by Horrax, G.; Yorshis, M., and Lavine, G. A.: Calcified Intradural Cholesteatoma of Unusual Size in a Patient Showing Manic-Depressive Symptoms, Arch. Neurol. & Psychiat. **33**:1058 (May) 1935; personal communication to the author.

4. Cushing, H.: A Large Epidermal Cholesteatoma of the Parieto-Temporal Region Deforming the Left Hemisphere Without Cerebral Symptoms, Surg., Gynec. & Obst. **34**:557, 1922.

tends to extend beneath the bone, between it and the dura mater. At operation one should, therefore, always explore the epidural space beneath the bone in order to be certain that all the tumor has been removed.

Through the kindness of the late Sir Percy Sargent, who supplied the notes concerning cases 2 and 3 from his personal records, and of Dr. Gordon Holmes I have been permitted to report the following three cases of intradiploic cholesteatoma which clearly illustrate the symptomatology, course, observations and proper treatment in cases of this rare tumor.

REPORT OF CASES

CASE 1.—*Swelling in right parietal region from before the age of 5 years. Slow increase in size. Asymptomatic until the age of 28, when convulsions appeared on the left side. Rachitic dwarf with defect in right parietal bone occupied by soft tumor and surrounded by bony ridge. Operation: removal of epidermoid of skull. Recovery.*

History.—R. W., a waiter, aged 28, was admitted to the service of Dr. Gordon Holmes at the National Hospital for Nervous Diseases on Feb. 10, 1931. He complained of a swelling on the right side of the head and of a convulsive seizure which had occurred on January 17. The patient stated that the swelling on the right side of the head was present prior to the age of 5 years, and his mother insisted that it was not present at birth. During the succeeding years it had grown slowly, but in no other way had its presence been manifested. It had often been struck while the patient was in school, in the boxing ring and elsewhere, but this had never been associated with any symptoms either local or general.

The family history was irrelevant. The patient had suffered from severe rickets in childhood, but otherwise his past history, except as noted, was unimportant.

Jacksonian Convulsion.—On January 17, while working at his trade as a waiter, the patient suffered from his first, and only, "fit." Warning of the approach of this attack was given by a sensation of "pins and needles" in the finger-tips of the left hand. This paresthesia then spread up the arm to the shoulder, into the left side of the neck and jaw. The left hand then contracted, the wrist and arm flexed, and the entire extremity was raised at the shoulder. At no time was there any tremor or clonic movement. The patient found himself unable to extend the arm, and the sensation of pins and needles continued. He then asked a fellow waiter to straighten his arm, and this endeavor caused pain in his neck and jaw. At this point in the attack the patient lost consciousness. This lasted a few seconds, and on recovery the arm was relaxed and the paresthesia was gone. There was, however, a feeling of stiffness in the left side of the neck and jaw, and they seemed drawn to the left. The patient also noted a dull ache in the swelling on the right side of the head. Observers stated that during the period of unconsciousness there was no convulsion but the patient became very dark. He soon recovered completely and consulted his physician who referred him to the National Hospital.

Examination.—The patient was a rachitic dwarf. The lower extremities were short and both, especially the right, were markedly bowed. When he was standing the finger-tips reached to the knees. Palpation of the skull revealed a soft fluctuant swelling in the center of the right parietal bone measuring 1½ by 1¼ inches

(3.7 by 3.1 cm.) and elevated about ¾ inch (1.9 cm.) above the plane of the surrounding tissues. The margins of the swelling were irregular and bony hard, and in the antero-inferior portion they projected above the level of the skull. There was very slight pulsation, and deep palpation elicited a cracking sound. Except for these findings the remainder of the physical examination gave negative results, and no evidence of involvement of the nervous system could be detected.

Lumbar puncture showed the cerebrospinal fluid pressure to be 195 mm. of fluid, and there were two cells per cubic millimeter and a total protein content of 50 mg. per hundred cubic centimeters of fluid.

The right lateral roentgenogram of the skull (fig. 1) disclosed a large ovoid defect in the upper half of the parietal bone. The margins were quite regular and slightly increased in density. The anteroposterior view (fig. 2) demonstrated the same defect. The separation of the inner and outer tables of the skull by the

Fig. 1 (case 1).—Right lateral roentgenogram of the skull. There is a large oval defect in the right parietal bone, the margins of which show a slight increase in density.

tumor was particularly well demonstrated. The inner table which formed the floor of the bony crater was depressed into the cranial cavity. The outer table had been completely eroded over a large area, but along the lower margin of the defect it formed an elevated overhanging ledge of bone. This was palpable clinically.

The patient was seen by Sir Percy Sargent, who immediately on examination and study of the roentgenograms made a diagnosis of cholesteatoma of the skull. The basis for his diagnosis was the recollection of two cases of intradiploic epidermoid in which he had performed an operation. In his cases there was a defect in the skull occupied by a soft tumor which arose within the diploe, separated the inner and the outer table of the skull and partially eroded the latter, thus producing a bony ridge about the opening.

Operation and Course.—On March 20, Sir Percy Sargent operated on the patient, making a semicircular flap of the scalp with the tumor at the center. This

was reflected, and beneath it was found a firm white cyst containing caseous white material. The cyst had excavated a circular crater about 2 inches (5 cm.) in diameter in the parietal bone. The cyst was readily enucleated. Beneath it was a very thin plate of bone, the inner table, which was greatly depressed and was broken by a stellate fracture. This inner table was removed, and lying between it and an irregularly thickened dura was more caseous material which was readily removed.

The patient made a complete recovery from the operation and was discharged on April 17.

Microscopic Examination.—A single section of the rolled-up wall of the cyst fixed in solution of formaldehyde and stained with hematoxylin and eosin (fig. 3) is available. The wall was composed of three distinct layers. The outermost was relatively acellular connective tissue which acted as the supporting

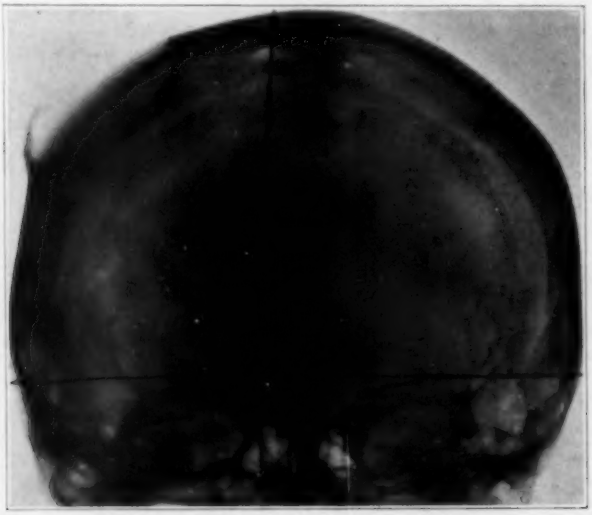

Fig. 2 (case 1).—Anteroposterior roentgenogram of skull. The defect is seen in about the middle of the right parietal bone. The neoplasm has separated the two tables of the skull. The outer table, which has been elevated above the surrounding bone, is partially eroded, the remaining antero-inferior portion forming an overhanging ledge. The inner table is intact and has been depressed into the intracranial cavity.

framework for the epithelial layer. Within this connective tissue were scattered fusiform and stellate fibroblasts, between which was a mass of intercellular fibers, reticulin and collagen. Throughout this layer were a few small blood vessels. Immediately internal to this lay the second layer, which was composed of a relatively thin stratified squamous epithelium. This layer was for the most part about six cells thick, though in places it increased to as much as fifteen or twenty cells. The deepest layer of this epithelium was composed of polyhedral or cuboidal cells arranged perpendicular to the plane of the epithelial layer. These cells corresponded to the malpighian cells in the basal layer of normal epidermis. Superficial to this layer the cells were much more flattened than those of normal epidermis and lay

parallel to the surface. The third layer consisted of cornified epithelium. It was composed of yellowish fibers arranged parallel to the surface and devoid of nuclei. The epithelial tissue was devoid of papillae and there were no dermal structures such as hair and glands. Microscopically this was a typical epidermoid.

In this case there was the typical history of long duration of a swelling of the scalp associated with a defect in the skull which was

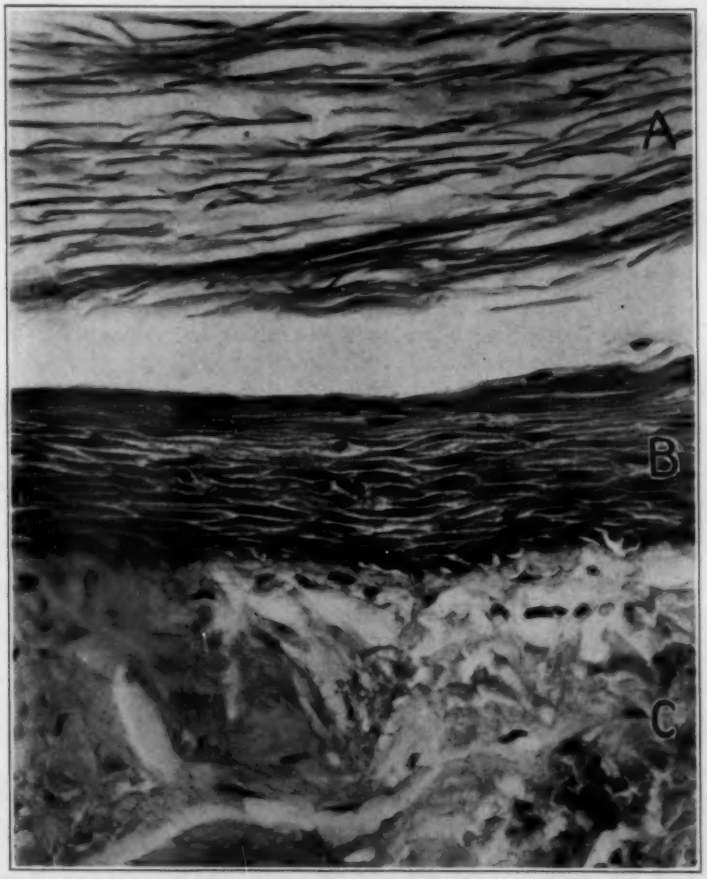

Fig. 3 (case 1).—Photomicrograph of the lining of the epidermoid cyst. Three layers are seen: *A* is composed of cornified epithelial cells which fill the interior of the cyst; *B* is a layer of stratified squamous epithelium, and *C* consists of relatively acellular connective tissue. Hematoxylin and eosin stain; × 380.

clearly demonstrable in the roentgenogram. It was unusual only in its association with a localized convulsive seizure which must be attributed to the effect of the tumor on the underlying central area of the right cerebral hemisphere. The microscopic picture was typical of these tumors.

CASE 2.—*Swelling in left frontal region of eighteen months' duration. Bony defect with raised bony margins. Operation: partial extirpation of cholesteatomatous epidermoid. Apparent recurrence three years later.*

C. G., a woman aged 26, first noted a swelling just to the left of the midline in the forehead eighteen months before consulting Sir Percy Sargent. This slowly increased in size until at the time of surgical intervention it measured 1½ inches in diameter. It had caused no other symptoms. Examination revealed a fluctuant swelling which did not pulsate and was not translucent. It was definitely surrounded by a ridge of bone. Roentgenograms revealed a rounded bony defect in the left frontal region.

Operation.—On Oct. 9, 1929, Sir Percy Sargent operated on the patient at St. Thomas's Hospital. The tumor lay in a bony crater with elevated margins in the frontal bone. The floor was depressed and very thin and was defective in the center. Through the opening the tumor was continuous with an endocranial portion which lay between the dura mater and the bone. Most of the caseous material was removed as well as the elevated bony margins of the crater and part of the inner table. The patient made an uneventful recovery and was discharged, returning to her work as a secretary.

Recurrence.—I was fortunate enough to see this patient in May 1931. She had remained in excellent health following the operation and continued satisfactorily with her work. She stated that following the operation the site of the tumor was depressed but subsequently this depression gradually filled in. Examination revealed a soft swelling in this region which was elevated slightly above the surrounding skin. The swelling presumably is a recurrence due to failure to extirpate the wall of the cyst completely.

Unfortunately no microscopic preparations are now available.

This case in all probability is indicative of the necessity of removing the entire cyst, contents and wall, at operation. If small portions of viable epithelium are left there must always be a danger that the tumor will recur.

CASE 3.—*Swelling in frontal region of many years' duration. Tumor resting in bony defect with raised bony margin. Operation: removal of intradiploic epidermoid. Recovery.*

E. S., a man aged 39, had long noted a swelling in the midline of the frontal region just above the bregma. This had apparently increased in size following a blow some time prior to his admission to St. Thomas's Hospital. There were no other symptoms.

Examination revealed a swelling in the middle of the forehead measuring 2½ inches (6.2 cm.) vertically and 1½ inches across which was elevated about 1 inch (2.5 cm.) above the surrounding tissue. A ridge of bone was palpable at the margins. This swelling was nonfluctuant and did not pulsate or transmit light. Apparently a roentgenogram was not made.

Operation.—On Jan. 29, 1930, Sir Percy Sargent operated on this patient and found a cyst lying in a bony crater. The cyst was readily shelled out and was found connected by a pedicle which passed through the thin, defective inner table to another collection of cholesteatomatous material within the skull. The cyst contained typical caseous material. The patient made an uneventful recovery and was soon discharged. Nothing is known of the subsequent course.

Unfortunately no microscopic preparations are available.

There can be little question of the nature of the neoplasm in cases 2 and 3 in spite of the absence of microscopic preparations. The clinical picture presented was typical of this condition, and the diagnosis was made by Sargent, who was thoroughly familiar with the appearance of such tumors.

In case 1, although the tumor had been subjected to repeated traumatic injury, the patient attached little significance to this fact. And there was no apparent relationship between injury and the growth of the neoplasm or the development of symptoms. In case 2 there was no mention of any injury. In the third case the patient, while not attributing the tumor to trauma, felt that an injury precipitated an increase in its size. It seems entirely unlikely that the growth of a neoplasm arising deep within the bone and explicable purely on the basis of an embryologic malformation should be precipitated by injury.

REVIEW OF THE LITERATURE

The first accurate description of a cranial epidermoid must be attributed to Cruveilhier,[5] in 1829, although it appears that Leprestre and Dupuytren had previously described such neoplasms. Nine years later, in 1838, Johannes Müller[6] in his excellent monograph described additional cases, among which was the first example of an intradiploic epidermoid to find its way into the literature. It is interesting to note that Müller observed the striking similarity between the contents of these cystic tumors and the cornified layer of the skin. He failed, however, to attribute these tumors to the epidermis correctly because of an incomplete examination of the walls of the cysts, which he thought consisted of acellular connective tissue. Remak[1] in 1854 was the first to correlate these neoplasms definitely with the epidermis, although his views regarding this association were not universally accepted until many years later.

Sixteen cases of epidermoid arising within the diploe have been described. These have been briefly summarized in the accompanying table. It will be noted that certain cases referred to by other writers as being instances of this type of growth have been omitted from the table. The case reported by Pfannmüller[7] was one of a subarachnoid epidermoid of the temporal lobe which did not involve the skull. In the

5. Cruveilhier, J.: Anatomie pathologique du corps humain, Paris, J. B. Baillière, 1829, vol. 2, pt. 1, plate 6.

6. Müller, Johannes: Ueber den feinen Bau und die Formen der krankhaften Geschwülste, Berlin, G. Reimer, 1838.

7. Pfannmüller, W.: Ueber das meningeale Cholesteatom, Inaug. Dissert., Giessen, C. von Munchow, 1896.

Cases of Intradiploic Epidermoid Tumor (Cholesteatoma) of the Skull Reported in the Literature

Author	Sex	Age When Diagnosed	Age at Onset	Region	Size	Symptoms	Erosion		Bony Ridge	Pulsation
							Outer Table	Inner Table		
1. Müller [6] (1838)	..	..	..	Occipital	.....	.....	Partial	+	..	..
2. Esmarch: Virchow's Arch f. path. Anat. **10**: 307, 1856	M	24	10	Left frontal	2.5 cm. high, 5.5 cm. in diameter	None	+	Broken	+	..
3. Weinlechner: Wien. klin. Wchnschr. **2**: 136, 1889	M	45	12	Left frontal	.....	Convulsions; headache	Small	+	..	+
4. Wotruba: Wien. klin. Wchnschr. **2**: 899, 1899	M	22	15	Right frontal	Goose egg	Headache; impaired vision by direct pressure on eye	+	+	..	..
5. Blecher: Deutsche Ztschr. f. Chir. **70**: 353, 1903	M	23	Since childhood	Left parietal	Hen's egg; 4.5 by 4 cm.	Headache	+	Small defect	+	0
6. Unterberger: Deutsche Ztschr. f. Chir. **81**: 90, 1906	F	16	2	Left sphenoid and frontal	.....	Headache	+	+	+	0
7. Cushing [4] (1922)	M	40	24	Left temporoparietal	3½ in. in diameter	? none	Small	+	+	+
8. Orlandi: Virchows Arch. f. path. Anat. **237**: 169, 1922	M	71	?	Right parietal	5 by 3 cm.	?	+	Small	+	?
9. Kempmann: Beitr. z. klin. Chir. **139**: 343, 1927	F	49	49	Left parietal	Palm of hand	0	+	+	+	?
10. Wertheimer: Fortschr. a. d. Geb. d. Röntgenstrahlen **38**: 656, 1928	M	38	Accidental finding	Right frontal and sphenoid	?	0	+	+	?	?
11. Alpers and Harrow: Am. J. Surg. **18**: 51, 1932	F	52	40	Right occipital	Large	Impaired vision, headache, nausea, vomiting	+	+	?	?
12. King [3]	M	28	23	Right temporoparietofrontal	7 by 5 by 4 cm.	Weakness left leg, blurred vision, diplopia, left hypesthesia	Partial	+	+	0
13. King [3]	M	26	25	Left occipital	110 Gm.; 7.5 by 8 cm. in roentgenogram	Headache, swelling in left occipital region	+	+	+	0
14. Bucy (case 1) 1934.....	M	28	5	Right parietal	1⅛ by 1¼ in.; elevated ¾ in.	Convulsion	+	Broken	+	Slight
15. Bucy (case 2) 1934.....	F	26	24	Left frontal	1½ by 1½ in.	Local swelling	+	Small	+	0
16. Bucy (case 3) 1934.....	M	39	Many years' duration	Midline frontal	2½ by 1½ in.; elevated 1 in.	Local swelling	+	Small	+	0

cases reported by both Körner [8] and Borchardt [9] the tumor was definitely stated to have arisen between the bone and the dura mater, not within the bone.

SUMMARY

Three cases of epidermoid tumor (cholesteatoma) arising within the diploe of the skull are reported. Such neoplasms are very rare, only thirteen having been recorded prior to the present report. These tumors, which arise from displaced anlagen of surface epithelium, expand the diploe and separate and erode the tables of the skull. The defect visible in the roentgenogram is typical of the condition. These intradiploic cholesteatomas rarely give rise to neurologic symptoms. The treatment is purely surgical. A permanent cure may be expected only if the tumor is completely removed.

8. Körner, O.: Ein Cholesteatoma verum in der hinteren Schädelgrube durch eine acute Mittelohreiterung inficiert und vereitert: Operation. Heilung, Ztschr. f. Ohrenh. **37**:352, 1900.

9. Borchardt, M.: Cholesteatom der hinteren Schädelgrube, Arch. f. klin. Chir. **77**:892, 1905.

ABERRANT PANCREATIC TISSUE IN THE GASTRO-INTESTINAL TRACT

A REPORT OF TWENTY-FOUR CASES

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AND

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The occurrence of aberrant pancreatic tissue, discovered either at operation or at autopsy, has been reported from time to time since the first case was described by Klob [1] in 1859. From that date until 1904, when Warthin [2] made the first comprehensive study of the literature, reports of isolated cases were published. Warthin collected forty-seven cases, to which he added two. Since then surveys of the literature have been made by Horgan [3] in 1921, by Simpson [4] in 1927 and by Hunt and Bonesteel [5] in 1934. The last review brought the total number of cases to one hundred and eighty-six. Since the completion of Hunt and Bonesteel's paper at least ten additional examples [6] have been reported, to which we are adding reports of twenty-four cases in which aberrant pancreatic tissue was found at various locations in the gastro-intestinal tract.

From the Departments of Surgery and Pathology of the Peter Bent Brigham Hospital, the Children's Hospital and the Harvard Medical School.

1. Klob, J.: Pancreas-Anomalien, Ztschr. d. Gesellsch. d. Aerzte z. Wein **15**:732, 1859.

2. Warthin, A. S.: Two Cases of Accessory Pancreas, Physician & Surg. **26**:337, 1904.

3. Horgan, E. J.: Accessory Pancreatic Tissue, Arch. Surg. **2**:521 (May) 1921.

4. Simpson, W. M.: Aberrant Pancreatic Tissue, in Contributions to Medicine and Surgery, dedicated to Aldred Scott Warthin, Ann Arbor, Mich., George Wahr, 1927, p. 435.

5. Hunt, V. C., and Bonesteel, H. T. S.: Meckel's Diverticulum Containing Aberrant Pancreas, Arch. Surg. **38**:425 (March) 1934.

6. (*a*) Best, R. R., and Bowers, W. F.: Anterior Hemipylorectomy for Aberrant Pancreatic Tissue of the Duodenum, Ann. Surg. **99**:967, 1934. (*b*) King, E. S. J., and MacCallum, P.: Pancreatic Tissue in the Wall of the Stomach, Arch. Surg. **28**:125 (Jan.) 1934. (*c*) Okinczyc, J.: Deux observations de pancréas aberrant, Bull. et mém. Soc. nat. de chir. **58**:1427, 1932. (*d*) Puhl, H.: Primäres Jejunalgeschwür mit heterotoper Fundusschleimhaut, Deutsche Ztschr. f. Chir. **239**:624, 1933. (*e*) Wertheimer, P.: Pancreas aberrant et gastrorragies, Bull. et mém. Soc. nat. de chir. **59**:243, 1933.

In the cases previously reported the most common site for the aberrant pancreatic tissue was in the upper portion of the gastro-intestinal tract, and in almost 80 per cent of the cases the anomaly was found in the wall of the stomach, duodenum or jejunum. In the majority of the remaining cases the aberrant pancreatic substance was located in the ileum, appearing particularly in diverticula of that portion of the small intestine. A few cases have been described in which pancreatic tissue occurred outside of the gastro-intestinal tract; in one case it occurred in the omentum,[2] in one in the mesenteric fat,[7] in one in an umbilical fistula,[8] in two in the wall of the gallbladder,[9] and in three in the splenic capsule.[10] Thus it is seen that in most instances the anomalous location of these fragments is in part derived from the foregut.

No explanation universally accepted has been given for the origin of aberrant pancreatic tissue. Zenker[11] attributed it to the formation of an additional pancreatic bud from the foregut which developed as an independent glandular mass and which had been carried away from its point of origin as the gut elongated. Glinski[12] interpreted the presence of the anomaly as a failure of a primitive anlage, probably the ventral bud or a part of it, to coalesce with the dorsal portion. Warthin[2] expressed the belief that accessory pancreatic tissue was formed from the lateral budding of the rudimentary pancreatic ducts as they penetrated the intestinal wall and that the mass of pancreatic tissue thus formed was snared off and carried upward or downward by the longitudinal growth of the intestine. This theory has had the support of Simpson.[4] Horgan[3] stated that buds of the pancreatic anlage attached themselves to any organ with which they came in contact and were carried away by growth or change in position. Moore[13] offered the

7. Thorel, C.: Histologisches über Nebenpankreas, Virchows Arch. f. path. Anat. **173**:281, 1903.

8. Wright, J. H.: Aberrant Pancreas in the Region of the Umbilicus, J. Boston Soc. M. Sc. **5**:497, 1901.

9. Cogniauz, P.: Contribution à l'étude des pancréas aberrants, Arch. franco-belges de chir. **31**:307, 1928. von Hedry, N.: Nebenpankreas in der Gallenblasenwand, Beitr. z. klin. Chir. **132**:570, 1924.

10. Ellis, A. G.: Accessory Pancreas, with Report of Two Cases, Proc. Path. Soc. Philadelphia **29**:25, 1908. Lubarsch, O.: Ueber das Vorkommen von Pankreasläppchen in der Milz, Virchows Arch. f. path. Anat. **254**:880, 1925. Weidman, F. D.: Aberrant Pancreas in the Splenic Capsule, Proc. Path. Soc. Philadelphia **31**:267, 1910.

11. Zenker, F. A.: Nebenpankreas in der Darmwand, Virchows Arch. f. path Anat. **21**:369, 1861.

12. Glinski, L. K.: Zur Kenntnis des Nebenpankreas und verwandter Zustände, Virchows Arch. f. path. Anat. **165**:132, 1901.

13. Moore, R. A.: Accessory Pancreases: Report of a Case with a Discussion of Their Pathology and Origin, Am. J. Path. **5**:407, 1929.

explanation that adhesions may cut across the main pancreatic anlage and isolate portions which can subsequently be implanted elsewhere. Taylor,[14] in his work on heterotopias of the alimentary tract, quoted Mathias,[15] Beutler[16] and Delhougne[17] as holding that accessory pancreatic tissue represents an atavistic phenomenon and reproduces a condition normally seen in certain lower animals and fishes, in which the pancreas is not a single organ but is diffusely scattered through the peritoneum and muscular coats of the intestinal wall. Recently King and MacCallum[6b] concluded that aberrant pancreatic tissue, which they had observed four times in the wall of the stomach, arose from the normal gastric epithelium under the action of abnormal stimuli. It was the thesis of these authors that the normal gastric mucosa undergoes a metaplasia to a pancreatic type of tissue when altered by chronic inflammatory changes.

Aberrant pancreatic tissue in the intestinal tract may apparently persist throughout life without producing clinical symptoms or pathologic changes, but occasionally it may give rise to one of several important lesions. This anomaly may act in a purely mechanical manner and cause either pyloric or intestinal obstruction. Such cases are reported by Albrecht and Artz,[18] Branham[19] and Hale.[20] Cases of intussusception wherein the pancreatic tissue has acted as the leading point have been reported by Benjamin,[21] Bize,[22] Brunner,[23] Hulst[24]

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14. Taylor, A. L.: The Epithelial Heterotopias of the Alimentary Tract, J. Path. & Bact. **30**:415, 1927.

15. Mathias, E.: Die Abgrenzung einen neuen Gruppe von Geschwülsten, Berl. klin. Wchnschr. **57**:444, 1920; Zur Kasuistik seltener Geschwulstbildungen, ibid., p. 398.

16. Beutler, A.: Ueber blastomatöses Wuchern von Pankreaskeimen in der Magenwand, Virchows Arch. f. path. Anat. **232**:341, 1921.

17. Delhougne, H.: Ueber Pankreaskeime im Magen, Arch. f. klin. Chir. **129**:116, 1924.

18. Albrecht, H., and Artz, L.: Beiträge zur Frage der Gewebsverirrung: II. Ueber die Bildung von dystrophischem Pankreas, Frankfurt. Ztschr. f. Path. **4**:167, 1910.

19. Branham, J. H.: Operative Treatment of Cancer of the Stomach, with Report of Six Partial Gastrectomies, Maryland M. J. **51**:144, 1908.

20. Hale, K.: Study of the Accessory Pancreas, with Report of One Causing Congenital Pyloric Stenosis, Ann. Surg. **83**:774, 1926.

21. Benjamin, A. E.: Accessory Pancreas with Intussusception, Ann. Surg. **67**:293, 1918.

22. Bize: Etude anatomo-clinique des pancréas accessoires situés à l'étrémité d'un diverticule intestinale, Rev. d'orthop. **5**:149, 1904.

23. Brunner, C.: Ein Beitrag zur Chirurgie und pathologischen Anatomie der Darminvagination, Beitr. z. klin. Chir. **25**:344, 1899.

24. Hulst, J. P. L.: Ueber einen in einem Darmdivertikel gelagerten Pankreaskeim mit sekundärer Invagination, Centralbl. f. allg. Path. u. path. Anat. **20**:12, 1909.

and Taylor.[14] Nauwerck,[25] Newmann [26] and Simon [27] expressed the belief that some intestinal diverticula are formed because of the weakening of the musculature of the intestinal wall by the presence of the aberrant pancreatic tissue at this point. This explanation has been a favorite one in describing the origin of many duodenal diverticula.

An inflammatory reaction of considerable magnitude may arise in aberrant pancreatic tissue. The symptoms of ulcer of the pylorus or duodenum may be closely simulated by an ulcerative process in the aberrant pancreatic tissue located at one of these sites. The presence of pancreatic tissue in such ulcers leads one to suspect that the anomalous substance so alters the normal relationships of the parts, or so changes the blood supply to the regional mucosa, that ulceration is prone to occur where this anomaly exists. Of the various pathologic processes which may be caused by the abnormality, superficial ulceration is the most common. Best and Bowers,[6a] Cave,[28] Cafritz,[29] Cohen [30] and Deaver and Reimann [31] reported the occurrence of such changes. It is well to bear in mind the possibility of such a lesion in cases of peptic ulcer. Inflammatory reaction in aberrant pancreatic tissue of a Meckel diverticulum or of some other intestinal diverticulum may give rise to symptoms closely resembling those of appendicitis. There are two reports, one by Hunt and Bonesteel [5] and a second by Thomson,[32] which record the occurrence of symptoms simulating those of appendicitis; in each case the symptoms were due to the fact that there was ulceration of the pancreatic tissue at the tip of a Meckel diverticulum.

A more rare condition which merits consideration in a study of this anomaly is the possibility of malignant change in the pancreatic tissue. The location of the lesion when the nodule projects into the intestinal lumen presents an excellent opportunity for irritative action which may lead through inflammation of a chronic type to neoplastic changes.

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25. Nauwerck, C.: Ein Nebenpankreas, Beitr. z. path. Anat. u. z. allg. Path. **12**:29, 1892.

26. Newmann, E.: Nebenpankreas im Darmdivertikel, Arch. d. Heilk. **11**:200, 1870.

27. Simon, H.: Beitrag zur Kenntnis der abgesprengten Pankreaskeime, Erlangen, E. T. Jacobs, 1905; quoted by Hunt and Bonesteel.[5]

28. Cave, H. W.: Aberrant Pancreatic Tissue Simulating Duodenal Ulcer, Am. J. Surg. **5**:537, 1928.

29. Cafritz, E. A.: Accessory Pancreatic Tissue, South. M. J. **22**:833, 1929.

30. Cohen, H.: Accessory Pancreas with Ulcer of Pylorus, Surg., Gynec. & Obst. **34**:384, 1922.

31. Deaver, J. B., and Reimann, S. P.: Surgical Treatment and Pathology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **32**:103, 1921.

32. Thomson, H. A.: Diverticula of the Intestinal Tract, Lancet **1**:860, 1908.

Instances of carcinomatous manifestations have been recorded by Branham,[19] Bookman [33] and Semsroth.[34]

These described lesions in aberrant pancreatic tissue are of interest to those dealing with the surgery and pathology of the gastro-intestinal tract. It is, however, no less important to recognize the nature of this anomalous tissue and to know that it may occur without giving rise to important changes. In the latter regard, it has been an unfortunate experience in several of our cases to mistake the tissue for a carcinomatous lesion of the stomach or intestine. The prolongation of the operation while removing benign pancreatic nodules and the danger of unnecessary opening of the intestine in these instances could have been obviated if the nature of the "nubbins" had been recognized at operation.

The following abstracts of twenty-four cases were collected from the records of the Boston Children's Hospital and the Peter Bent Brigham Hospital. These cases are summarized in the table.

REPORT OF CASES

CASE 1.—R. C., a girl aged 8 days, entered the hospital for treatment of a spina bifida and an infected meningocele. Death ensued from meningitis.

Gross Pathologic Description.—In the midportion of the jejunum there were two nodular masses lying within the wall of the intestine which projected into the lumen of the jejunum. The largest of these measured 4 mm. in diameter and was elevated to form a flattened projection 3 mm. in height. The mucosa covered this tissue, and there was no ulceration or evidence of inflammation in the area. The second nodule in the jejunum was approximately 3 mm. in diameter and 2 mm. in thickness and was covered by mucosa.

Microscopic Examination.—The "nubbins" of aberrant tissue lay wholly within the submucosa (fig. 1). This anomalous tissue had the general histologic picture of normal pancreatic tissue with regard to acinar structure, ductules and stroma, but islets of Langerhans cells were missing. There was no inflammatory reaction in the nodules. The mucosa over these masses was largely destroyed by postmortem autolysis, but there was no regional evidence of inflammatory reaction.

CASE 2.—E. D., a girl aged 2 weeks, entered the hospital after an illness of twenty-four hours and died of bacteremia, bronchopneumonia, acute bronchitis and tracheitis.

Gross Pathologic Description.—Fifty centimeters above the ileocecal valve there was a Meckel diverticulum which measured 3.5 cm. in length. There was no inflammatory change of the mucosa lining the diverticulum. On the outer surface of the diverticulum, and covered by serosa, there was a thin, grayish-white, flat nodule about 0.5 cm. in diameter. This appeared to be accessory pancreatic tissue.

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33. Bookman, M. R.: Carcinoma of Duodenum Originating from Aberrant Pancreatic Cells, Ann. Surg. **95**:464, 1932.

34. Semsroth, K.: Histologic Interpretation of Certain Carcinoids of Small Intestines; Neoplasm-Like Malformation of Tissue of Pancreas, Arch. Path. **6**:575 (Oct.) 1928.

Microscopic Examination.—The mucosa of the diverticulum resembled the type of mucosa found in the small intestine, but there was no distinct muscularis mucosae. The submucosa was represented by only a few strands of connective tissue.

Summary of Cases of Aberrant Pancreatic Tissue Occurring in the Gastro-Intestinal Tract

Case	Age	Sex	Location of Aberrant Pancreatic Tissue	Size of Mass of Aberrant Pancreatic Tissue	Pathologic Change	Pancreatic Tissue Found at
1	8 days	F	Jejunum (2 nodules)	4 mm. diameter 3 mm. diameter	None	Autopsy
2	2 weeks	F	Meckel diverticulum	5 mm. diameter	None	Autopsy
3	4 weeks	F	Pyloric ring	3 mm. diameter 2 mm. thickness	None	Autopsy
4	7 weeks	M	Meckel diverticulum	8 mm. diameter	None	Autopsy
5	3 months	M	Jejunum	7 mm. diameter 4 mm. thickness	None	Autopsy
6	3 months	M	Ilium	1 cm. diameter 4 mm. thickness	None	Autopsy
7	10 months	M	Duodenum	1.2 cm. diameter	Ulcer with hemorrhage	Autopsy
8	1 year	F	Meckel diverticulum	1.5 cm. diameter 6 mm. thickness	None	Autopsy
9	3 years	M	Duodenum	7 mm. diameter 4 mm. thickness	None	Autopsy
10	4 years	F	Meckel diverticulum	6 mm. diameter 2 mm. thickness	None	Operation
11	7 years	F	Meckel diverticulum	5 mm. diameter 3 mm. thickness	None	Autopsy
12	9 years	M	Meckel diverticulum	5 mm. diameter 3 mm. thickness	None	Autopsy
13	11 years	F	Jejunum	8 mm. diameter 4 mm. thickness	None	Autopsy
14	33 years	M	Duodenum	1.3 cm. diameter 5 mm. thickness	None	Autopsy
15	50 years	M	Duodenum	7 mm. diameter 4 mm. thickness	None	Autopsy
16	54 years	F	Stomach	Many "nubbins" 2-4 mm. diameter	Ulcer	Operation
17	58 years	F	Duodenum	2 cm. diameter 6 mm. thickness	None	Operation
18	58 years	M	Duodenum	5 mm. diameter 3 mm. thickness	None	Operation
19	58 years	M	Duodenum	1 cm. diameter 3 mm. thickness	None	Autopsy
20	60 years	M	Jejunum	3 by 2 cm. 5 mm. thickness	None	Autopsy
21	65 years	F	Duodenum	1.5 cm. diameter 7 mm. thickness	Ulcer with hemorrhage	Autopsy
22	66 years	F	Pylorus	Spherical 1 cm. diameter	Obstruction of pylorus	Operation
23	69 years	M	Duodenum	7 nodules 1-9 mm. diameter	None	Autopsy
24	82 years	F	Duodenal diverticulum	Capped diverticulum	None	Autopsy

External to the musculature there was a flattened "nubbin" of pancreatic tissue which was covered by serosa (fig. 2). This aberrant substance was histologically the same as normal pancreas, except for the fact that no islets of the Langerhans type were present. The ducts were small and not dilated. They were lined by a cuboidal type of epithelium. There was no communication between these structures and the lumen of the diverticulum in the sections studied. There was no inflammatory or cicatricial process in any part of the diverticulum.

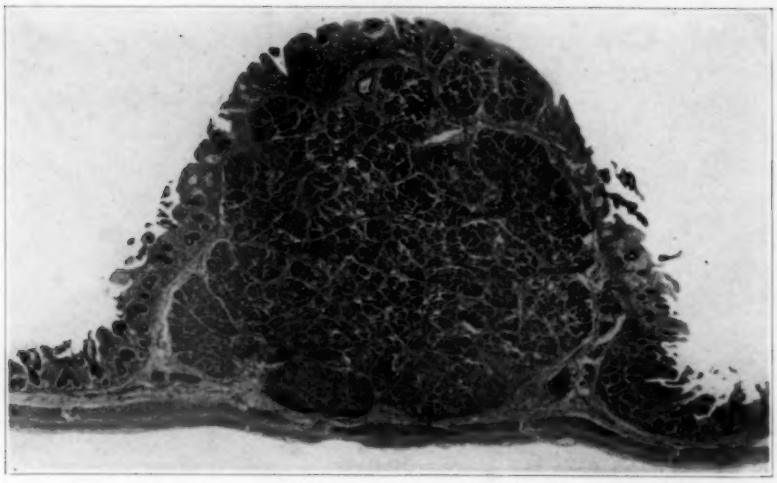

Fig. 1 (case 1).—Photomicrograph (× 15) of aberrant pancreatic tissue occurring in the wall of the jejunum. The pancreatic substance is covered internally by mucosa and externally by intestinal muscularis.

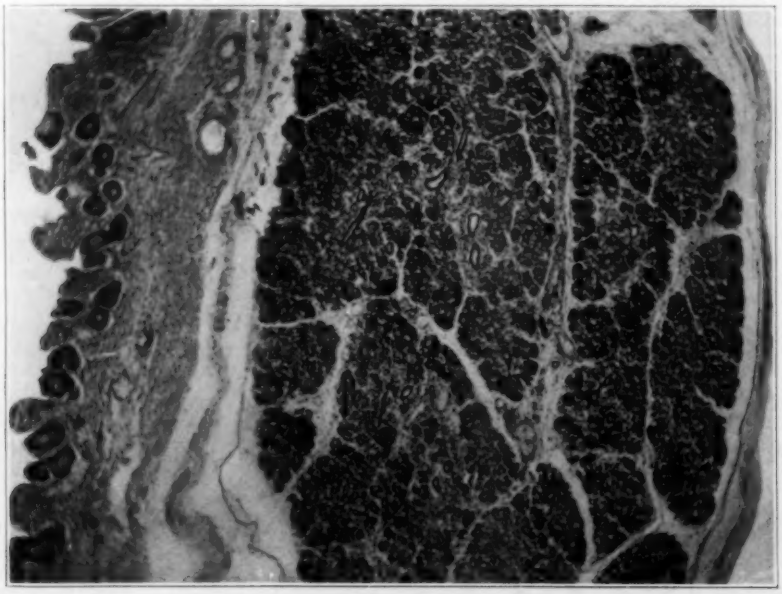

Fig. 2 (case 2).—Photomicrograph (× 20) of pancreatic tissue occurring in the wall of a Meckel diverticulum.

CASE 3.—E. B., a girl aged 1 month, entered the hospital on Sept. 26, 1926, because of difficulty in breathing of one day's duration. The results of physical examination and the clinical course indicated congenital cardiac disease. The patient died three days after admission.

Gross Pathologic Description.—Just at the pylorus a small mass was felt in the wall at the superior border of the pyloric ring. Proximal to the ring along the lesser curvature of the stomach was an elevation of the mucosa about 2 mm. in height and 3 mm. in diameter. This resembled a small nipple and at its tip presented a small mouth about 1 mm. in diameter. In the wall of the stomach beneath the site of this projection there was a nodule 8 mm. in diameter. When this was sectioned a glistening, pearly white surface was exposed.

Microscopic Examination.—Lying almost entirely within the muscularis of the pylorus there were islands of pancreatic tissue which were separated from one another by intervening bundles of the smooth musculature. This aberrant substance consisted of pancreatic acinar cells grouped into small lobules and intermixed with a few small ducts lined by cuboidal cells. There were no islets of the Langerhans type. The ducts of this nodule connected with larger ducts coursing out in the submucosa. The latter ducts were lined by columnar cells and apparently communicated with the intestinal lumen.

CASE 4.—C. H., a boy aged 7 weeks, entered the hospital for treatment of cellulitis of the face, abdomen and thigh. He died nine days later. The past history had been essentially irrelevant, and there had been no evidence of gastrointestinal abnormality.

Gross Pathologic Description.—In the terminal ileum there was a Meckel diverticulum measuring 2 cm. in length. At its tip there was a spherical mass of rather firm tissue 8 mm. in diameter. There was no evidence of ulceration or inflammatory change within the mucosa of the diverticulum.

Microscopic Examination.—The aberrant pancreatic tissue was situated within the submucosa and divided the muscularis into separate bands. It was covered on its inner aspect by normal mucosa of the type found in the ileum and on the outer surface by a thin serosa. The general appearance of the tissue resembled that of normal pancreatic acinar substance, except that it was divided into lobules by the bands of smooth muscle. In addition, there were large dilated ducts, having an almost acinar form, which were lined by columnar epithelium. There were no cells of the Langerhans islet type. The stroma was scanty, and there was no inflammatory reaction.

CASE 5.—Q. V., a boy aged 3 months, entered the hospital on July 3, 1922, because of jaundice of one week's duration. The clinical diagnosis was jaundice, secondary to generalized sepsis. Death ensued three days later.

Gross Pathologic Description.—In the jejunum there was a firm, gray, flattened nodule beneath the visceral peritoneum. This measured approximately 0.7 cm. in diameter and 4 mm. in thickness.

Microscopic Examination.—The nodule almost completely replaced the musculature but was pierced in a few places by small bundles of the circular fibers. The aberrant tissue consisted of a compact structure with general histologic features closely resembling those of normal pancreatic tissue except for the absence of islets. The acinar structures were supplied by a few small ducts. The nodule was covered on a portion of its external surface by some fibers of longitudinal intestinal musculature, but for the most part it was covered only by a thin serosa. The mass projected up to the muscularis mucosae but did not extend into the

mucosa. The intestinal mucosa over the nodule was intact and showed no inflammatory change, ulceration or scarring. There was no inflammatory reaction in the pancreatic substance.

CASE 6.—J. J. T., a boy aged 3 months, entered the hospital on Sept. 15, 1923, because of persistent diarrhea, vomiting and drowsiness of three days' duration. Bronchopneumonia and bilateral otitis media developed, and the child died fourteen days later.

Gross Pathologic Description.—In the first portion of the ileum, a "nubbin" was found in the intestinal wall. This was 1 cm. in diameter and 0.4 cm. in thickness. It lay on the antimesenteric side of the intestine. It was firm, slightly grayish and finely lobulated.

Microscopic Examination.—The nodule partially replaced the musculature but was pierced in a few places by fine strands of the intestinal muscularis. Only the serosa covered the outer surface. The inner border extended up to the muscularis mucosae. The overlying intestinal mucosa showed no important variation from the normal. The pancreatic tissue had the general histologic structure of normal pancreatic tissue except for the few intervening muscle fibers and the absence of Langerhans islets. The general arrangement of acinar cells and the form of the ducts resembled the respective features of normal pancreatic tissue. Secretory material could be seen in the ducts. There was no opening of the ducts to the intestinal lumen in the sections studied. There was no inflammatory reaction or scarring.

CASE 7.—E. A., a boy aged 10 months, was admitted to the hospital on Feb. 10, 1917, for treatment of a postauricular abscess. Subsequently bronchopneumonia and pleuritis developed, and the patient died sixteen days later. No intestinal abnormality was suspected.

Gross Pathologic Description.—The duodenum was filled with a reddish-black friable blood clot. On the superior wall of the duodenum and about 1 cm. below the pylorus there was an area of reddening and ulceration 1 cm. in diameter. The base of this was granular and mottled. The margins and base of this area of ulceration were not indurated, but they were slightly elevated. At the base of the aforementioned area and presenting on the serosal surface of the duodenum, there was a firm, flattened nodule 1.2 cm. in diameter and 4 mm. in thickness. The external surface of this nodule was pinkish gray and finely lobulated. Partially changed blood was present throughout the entire intestinal tract.

Microscopic Examination.—The muscularis was intact throughout the section and maintained a normal uninterrupted double-layered form. About half of the aberrant pancreatic tissue lay outside of the muscularis and was covered by serosa. The remaining half lay inside of the muscularis and extended up to the Brunner glands of the duodenum. The histologic structure of the aberrant tissue resembled that of normal pancreatic tissue with respect to the arrangement of acinar cells, amount of stroma, distribution of ducts and presence of Langerhans islets. External to the muscularis there was no inflammatory process, but inside of the muscle layer there was an acute necrosis of pancreatic tissue, intestinal submucosa and mucosa with evidence of hemorrhage, ulceration and deposition of fibrinoid material. The area was moderately infiltrated with polymorphonuclear leukocytes. There was no evidence of organization. There was no scarring indicative of old healed ulceration or inflammatory process.

CASE 8.—B. J. W., a girl aged 1 year, had a history of having had a respiratory infection for twelve days, followed by convulsions and fever. She died twelve hours after admission.

Gross Pathologic Description.—A Meckel diverticulum, 2 cm. in length, was found 75 cm. above the ileocecal valve. In the wall of the diverticulum there was a pinkish-gray nodule which measured 1.5 cm. in diameter and 0.6 cm. in thickness. On section it had a lobular structure and appeared to be accessory pancreatic tissue. The mucosa of the diverticulum showed no inflammatory change.

Microscopic Examination.—The mucosa of the diverticulum was essentially gastric in type, and large numbers of parietal cells were seen intermixed with the chief cell type. A portion of the mucosal lining resembled that of the ileum. The mucosa in some areas was thrown into prominent folds; elsewhere it was flattened and the glandular elements were missing. On one side of the wall of the diverticulum was the previously described nodule of pancreatic tissue. This lay wholly outside of the muscularis and was covered by serosa (fig. 3). This tissue closely

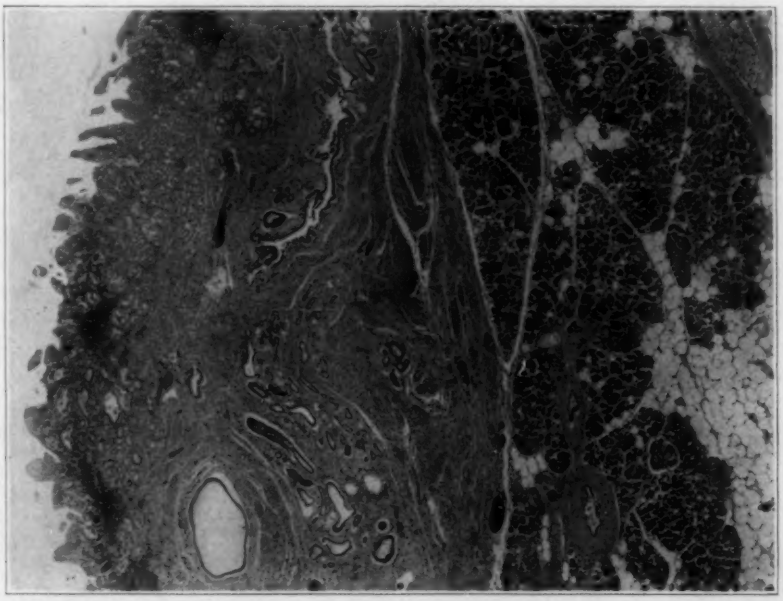

Fig. 3 (case 8).—Photomicrograph (× 15) of pancreatic substance occurring in the wall of a Meckel diverticulum. Toward the right there is acinar tissue scattered through which are several Langerhans islets. In the central portion of the photomicrograph are irregular ducts of varying size, many of which are dilated. The lumen of the diverticulum is toward the left.

resembled normal pancreatic substance in regard to general arrangement of acinar tissue, islet structures, ducts and stroma. The Langerhans islets were rather numerous.

Case 9.—L. F., a boy aged 3 years, entered the hospital on Oct. 19, 1917, for treatment of pneumonia and died the same day.

Gross Pathologic Description.—In the wall of the duodenum was a nodule 7 mm. in diameter and 4 mm. in thickness. This was firm and finely lobulated; the inner surface was covered by mucosa; externally the nodule was covered by serosa. The "nubbin" imparted a light grayish color to the intestinal epithelium and serosa.

Microscopic Examination.—The major part of the aberrant tissue lay between the muscularis and the Brunner's glands. There was, in addition, a thin layer of pancreatic substance between the intact muscularis and the serosa. The tissue resembled that of normal pancreas in all respects. There were many islets of Langerhans cells (fig. 4). There were no inflammatory changes or scarring. The overlying mucosa was normal.

CASE 10.—C. C., a girl aged 4 years, entered the hospital on Feb. 20, 1930. She had been ill for four days with what proved to be appendicitis with perforation. At operation a gangrenous appendix was removed and a Meckel diverticulum was resected. The patient was discharged as cured on March 24.

Gross Pathologic Description.—The Meckel diverticulum measured 3 cm. in length and 1 cm. in diameter. The entire diverticulum was diffusely hemorrhagic

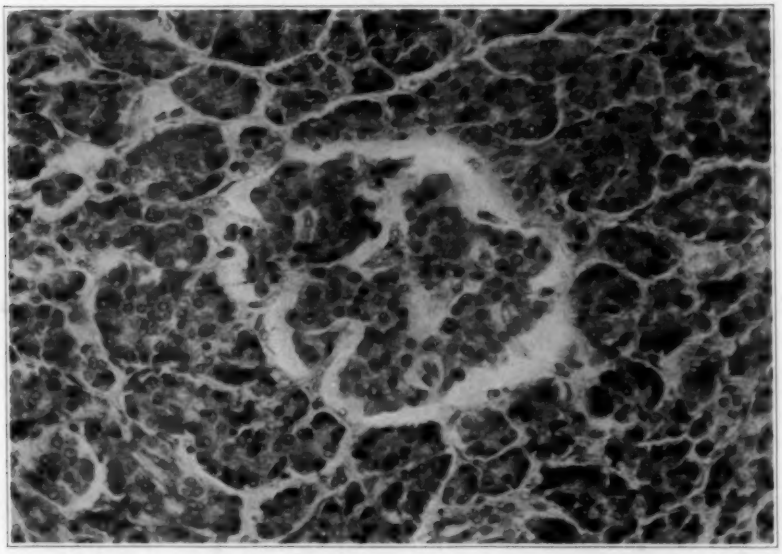

Fig. 4 (case 9).—Photomicrograph (× 200) of pancreatic tissue occurring in the wall of the duodenum, showing normal acinar structures and an islet of Langerhans.

and congested. At the apex of the diverticulum there was a small rounded lesion 6 mm. in diameter and 2 mm. in thickness which apparently lay within the submucosal layer. The mucosa over this was intact and showed no ulceration. This nodule was pinkish gray and firm and on cross-section had a faint lobular appearance.

Microscopic Examination.—The mucosa of the diverticulum was entirely of the type found in the ileum. Within the muscularis there was a nodule of aberrant tissue which had the histologic structure of normal pancreatic tissue except for the absence of islets of Langerhans cells. The number and size of ducts, arrangement of acini and amount of stroma were of the proportion seen in the normal pancreas. There was no inflammatory reaction within the nodule of pancreatic tissue, but on the serosal surface of the diverticulum there was an acute fibrino-

hemorrhagic and purulent exudate indicative of peritonitis (secondary to ruptured appendicitis). The mucosa was intact in the nodule and showed no ulceration or scarring.

CASE 11.—P. J., a girl aged 7 years, entered the hospital on Nov. 27, 1931, after an illness of one week which proved to be meningitis. Laboratory studies showed the causative organism to be a pneumococcus. The patient died four days after entry.

Gross Pathologic Description.—A Meckel diverticulum was found 1 meter above the ileocecal valve. It was approximately 4 cm. in length and 1.5 cm. in diameter. On one side of the diverticulum was a small, flattened "nubbin" 5 mm. in diameter and 3 mm. in thickness. This was pinkish gray and was covered by serosa. The mucosa of the diverticulum was intact and showed no ulceration or scarring.

Microscopic Examination.—In the wall and scattered through the muscularis and beneath the serosa of the diverticulum there was a small mass of tissue which had the histologic structure of normal pancreatic tissue except that there were no Langerhans islets. There was no inflammatory reaction in this pancreatic tissue. The mucosa of the diverticulum was gastric in type.

CASE 12.—H. M., a boy aged 9 years, entered the hospital on Aug. 29, 1931, and died on September 2. For four days before admission the patient had symptoms suggestive of meningitis. The course while he was in the hospital and the findings showed an influenzal meningitis. The past history was entirely irrelevant. There had been no previous symptoms referable to the gastro-intestinal tract.

Gross Pathologic Description.—Routine examination disclosed a Meckel diverticulum about 1.5 meters proximal to the ileocecal valve. The Meckel diverticulum was 3 cm. long and 1.5 cm. in diameter. The mucosa was smooth. The serosal surface was also smooth and unbroken except at the tip of the diverticulum where there was a small "nubbin" of tissue 5 mm. in diameter and 3 mm. in thickness beneath the serosa. The cut surface of this nodule had a faint lobulation and was pale pinkish gray.

Microscopic Examination.—The epithelium of most of the diverticulum was similar to that normally found in the ileum. The mucosal epithelium overlying the aberrant tissue was gastric in type and contained many parietal cells. Lying within the muscularis of the diverticulum (which elsewhere consisted of two layers) there was pancreatic tissue which was divided into lobules by bundles of the muscular layer. The external surface was covered by serosa. The pancreatic substance consisted of intermixed acinar tissue and ducts of varying size. The epithelium of the duct was mostly cuboidal, but a small portion was low columnar. Some of the ducts were dilated. Several ducts passed up through the mucosa and connected with the lumen of the diverticulum by way of the gastric glands. The acinar tissue was similar in appearance to that found in normal pancreatic tissue. There were no islets of Langerhans cells. The stroma was moderately dense. There was no inflammatory reaction.

CASE 13.—H. D., a girl, aged 11 years, entered the hospital on Oct. 24, 1929, after an illness of one week which proved to be miliary tuberculosis and tuberculous meningitis.

Gross Pathologic Description.—In the upper portion of the jejunum there was a small nodule within the intestinal wall which was approximately 8 mm. in diameter and 4 mm. in thickness. This was covered by mucosa, and the surface was not ulcerated. The tissue was grayish pink and firm and had a faint lobular appearance on cross-section.

Microscopic Examination.—The aberrant pancreatic tissue lay entirely within the submucosa. The mucosa was intact over the nodule and did not show any inflammatory reaction or ulceration. The pancreatic substance resembled normal pancreatic tissue except for the absence of islets of Langerhans cells. The acinar structures had the usual lobular arrangement. The smaller ducts were lined by cuboidal epithelium. A few of the larger ducts were dilated and were lined by a columnar epithelium.

Case 14.—J. M., a man aged 33, was admitted to the hospital on June 9, 1928, with the complaint of abdominal pain and distention of three weeks' duration. A diagnosis of subacute bacterial endocarditis due to Streptococcus viridans was made. The patient's condition rapidly became worse, and he died on June 15.

Gross Pathologic Description.—A mass projecting on the external surface of the intestine was found on the anterior wall of the first part of the duodenum. This mass was 1.3 cm. in diameter and 0.5 cm. in thickness. It was light gray, was slightly lobulated and grossly resembled pancreatic tissue. It was entirely covered by serosa. The mass did not project into the intestinal lumen but could be seen beneath the normal-appearing, nonulcerated mucosa.

Microscopic Examination.—The nodule of aberrant tissue lay partially within the submucosa but mostly within the muscular layer of the intestine. The fibers of the muscularis were separated and coursed as isolated bundles through the pancreatic tissue. The mucosa was intact over the area, and the serosa was unbroken. The aberrant tissue consisted partially of a dense fibrous stroma in which there were many isolated ducts of varying size. The smaller ones were lined by cuboidal epithelium, and the larger ones, by columnar epithelium. In one small area there were glands of the Brunner type which merged into and connected with the ductal system. Scattered between the ducts were islands of pancreatic acinar tissue which had the general appearance of normal pancreatic substance. A small number of islets of the Langerhans type were seen. A few lymphoid cells were scattered through the stroma, but there was no active inflammatory process.

Case 15.—M. B., a man aged 50, entered the hospital on March 25, 1932, because of cerebral hemorrhage. In spite of repeated removal of spinal fluid by lumbar puncture the patient's condition did not improve, and death occurred twenty-five days after admission.

Gross Pathologic Description.—In the wall of the duodenum a small, slightly raised nodule was found beneath the mucosal surface. This was 7 mm. in diameter and 4 mm. in maximum thickness. It was slightly lobulated, firm and pinkish gray. There was no ulceration of the overlying mucosa.

Microscopic Examination.—The aberrant pancreatic tissue lay entirely between the mucosa and the muscularis and almost completely replaced the Brunner glands in this area. There was no distinct muscularis mucosae; hence the pancreatic tissue abutted against the bases of the mucosal glands. Most of the tissue resembled closely the lobular, acinar structure of normal pancreatic tissue. A few normal-appearing islets of the Langerhans type were found. For the most part the stroma was of the same prominence as that found in normal pancreatic tissue, but in one deep area there was a dense stroma through which coursed numerous small ducts unaccompanied by acinar or islet elements.

Case 16.—H. C., a woman aged 54, was admitted to the hospital on March 16, 1930, because of irregular vaginal bleeding of six months' duration. The past history was entirely irrelevant. A diagnosis of adenocarcinoma of the fundus was made; this was substantiated by microscopic examination of curetted material. On

March 17, 1930, a hysterectomy was performed by Dr. John Homans. Examination of the upper portion of the abdomen revealed a slightly umbilicated mass 1.5 cm. in diameter and 1 cm. in depth in the anterior surface of the gastric wall just proximal to the pylorus. This was thought to be a carcinoma in an early stage of development, and resection of this portion of the stomach was carried out. The patient's postoperative course was not remarkable.

Gross Pathologic Description.—At the line of junction between the duodenal and the gastric mucosa there was an ulcer which measured 1 cm. in diameter and 5 mm. in depth. It was sharply punched out and had well defined borders. Surrounding the ulcer there was cicatrization of the gastric wall in a zone varying from 5 to 10 mm. in width. Around the margin of the ulcer the mucosa was grayish pink and presented numerous small grayish-white elevations distinctly different in appearance from the surrounding mucosa. These elevations were firm and measured about 2 mm. in diameter. They were elevated 2 mm. above the surface of the surrounding mucosa.

Microscopic Examination.—In the gastric submucosa and extending down through the musculature there were islands of pancreatic tissue which were from 1 to 4 mm. in greatest dimensions. Bundles of gastric musculature coursed between the lobules of pancreatic substance. Smooth musculature and serosa covered the exterior of these nodules. This aberrant tissue had the appearance of normal pancreatic parenchyma. It consisted mostly of normal sized acini in lobular arrangements and was supported by a fine fibrous stroma. Small ducts coursed through this tissue. These were within the range of number and size found in normal pancreatic tissue. They were all lined by a cuboidal epithelium. A few islets of Langerhans were found. Extending along the external surface of the nodules was a layer about 2 mm. in thickness in which there were numerous ducts which were set in a dense stroma. These ducts, which were not accompanied by any cells of the acinar or islet type, varied greatly in size, some having a barely discernible lumen and others being large and dilated (fig. 5). Gradations in size between these two extremes were seen. Most of the epithelium was cuboidal, but in the larger ducts columnar epithelium was frequently seen. Slight scarring had replaced some of the pancreatic tissue, but in view of the adjacent ulceration the area was surprisingly free from any active inflammatory reaction. Small accumulations of lymphoid cells and occasional lymphoid germinal follicles were seen beneath the mucosal glands.

Case 17.—D. Y., a Negress aged 58, entered the hospital on April 28, 1933, complaining of epigastric pain of three years' duration. For three months before admission the patient had vomited daily, and she had passed black stools during the same period. The patient became gradually weaker and lost 35 pounds (15.9 Kg.) in weight. Physical examination showed a well developed but poorly nourished Negress in some distress. Except for slight tenderness in the epigastrium the examination gave no remarkable results. Roentgen studies of the stomach showed an irregularity and narrowing of the distal 4 cm. of the antrum; this was interpreted as representing a carcinoma. Routine studies of the blood and urine gave normal results. Gastric analysis showed free hydrochloric acid equivalent to 43 cc., and total acidity equivalent to 64 cc., of tenth-normal sodium hydroxide. All specimens of gastric contents gave positive reactions to the benzidine test. The Wassermann and Hinton tests of the blood were negative.

Operation.—On April 29, 1933, Dr. Elliott C. Cutler resected the antral portion of the stomach for carcinoma.

Gross Pathologic Description.—The surgical specimen consisted of the antral end of the stomach, the pylorus and the first part of the duodenum. On the greater gastric curvature there was a neoplasm which later proved to be an adenocarcinoma. On the posterior wall of the first portion of the duodenum there was a rounded, raised nodule presenting on the outer surface of the intestine. This was 2 cm. in diameter and 6 mm. in thickness. It was covered by serosa. This tissue was slightly lobulated, was pinkish gray, and on cross-section had the general appearance of pancreatic tissue.

Microscopic Examination.—The aberrant pancreatic tissue lay almost wholly outside of the intestinal musculature, but a few small islands of this tissue were found between the muscle bundles. The outer surface of the specimen was covered by a normal serosa. The pancreatic tissue had essentially the same histologic fea-

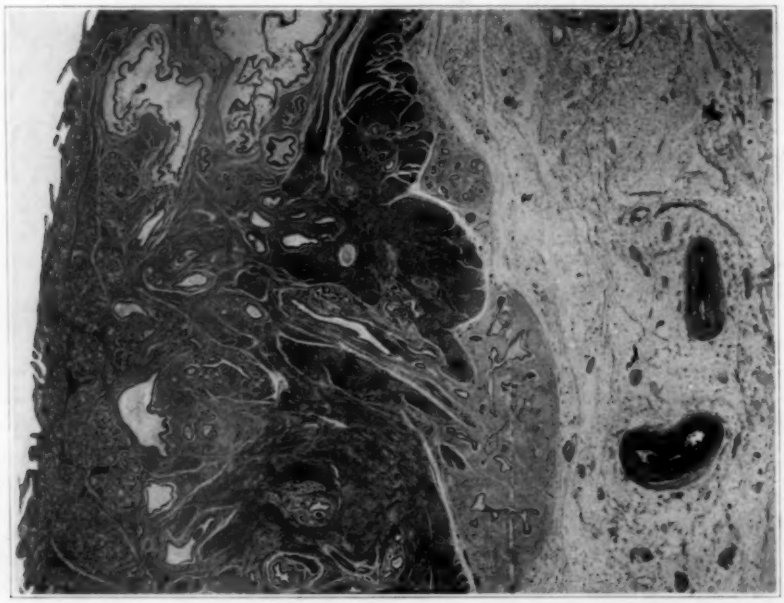

Fig. 5 (case 16).—Photomicrograph (× 12) of an aberrant nodule occurring in the wall of the stomach, illustrating anomalous ducts of variable size lying within the submucosa. (Other areas in the same specimen showed typical acinar and islet tissue.)

tures as those found in normal pancreas. There was the usual arrangement of acinar and islet substance. The smaller ducts connected with larger ones, lined with columnar tissue, which emptied into the intestinal lumen. The mucosal epithelium and Brunner's glands showed no evidence of inflammatory reaction or cicatrization.

Case 18.—J. S., a man aged 58, entered the hospital in November 1932 with the complaint of periodic vomiting of one year's duration. Two years before admission mild distention after meals began to develop; this became progressively worse until the time of hospitalization. There was no history of hematemesis. During the present illness the patient lost 15 pounds (6.8 Kg.). Physical examination showed him to be well developed and fairly well nourished. He vomited

several times during the examination. Except for a slight enlargement of the liver, the physical examination gave negative results. Roentgen studies of the gastrointestinal tract showed that the stomach was low, dilated and atonic. There was an irregularity involving the pyloric sphincter, and no barium sulphate was seen to pass from the stomach during examination. The findings indicated an obstructive lesion of the pylorus which was thought to be a carcinoma.

Operation.—On Nov. 5, 1923, Dr. David Cheever resected the antral portion of the stomach because of an extensive adenocarcinoma. At the time of operation a rounded mass of white tissue 5 mm. in diameter was discovered beneath the serosa on the anterior surface of the second part of the duodenum. This was thought to be a metastasis from the gastric carcinoma, and hence a portion of the duodenum was excised.

Gross Pathologic Description.—The first specimen consisted of the resected portion of the stomach and included the carcinoma. The second specimen consisted of a portion of duodenal wall which was about 1.5 cm. in diameter. In the center of this was a small rounded, flattened nodule about 5 mm. in diameter and about 3 mm. in thickness which was situated within the muscular layer of the intestinal wall. It was completely covered on its inner surface by mucosa and on its external surface by serosa. The nodule was slightly lobulated, firm but not hard and pinkish white.

Microscopic Examination.—The nodule lay totally within the duodenal musculature, which was expanded to surround it. Muscle bundles also coursed through the nodule in a trabecular arrangement, breaking the nodule into isolated islands. The serosa, submucosa and mucosa were normal and intact. The islands of aberrant tissue consisted largely of groups of ducts of varying type. Some of these were lined by tall columnar epithelium; others were lined by cuboidal epithelium. The ducts were relatively small, and no material was present in their lumens. These ducts did not communicate with the intestinal lumen in the sections studied. Some of the islands in the aberrant tissue consisted largely or wholly of cells in acinar arrangement and similar in appearance to normal pancreatic acinar substance. There were no tissues similar to islets of Langerhans cells. There was no inflammatory reaction in the nodule.

Case 19.—S. H., a man aged 58, entered the hospital on Jan. 23, 1934, complaining of weakness of eight weeks' duration. There was a history of gradual swelling of the lymph glands of the right side of the neck for the past three years. The patient's condition became progressively worse, and death occurred on Feb. 3, 1934.

Gross Pathologic Description.—Autopsy disclosed a lymphoblastoma of the Hodgkins type with infiltrations of the spleen, liver, kidneys, abdominal and cervical lymph nodes and bone marrow. On the medial surface of the duodenum, 5 cm. below the pylorus, there was a nodule 1 cm. in diameter which was rough, rather firm, well defined and raised 3 mm. above the surrounding duodenal mucosa. The nodule was covered by normal-appearing mucosa.

Microscopic Examination.—There was no ulceration or inflammatory change of the mucosa or duodenal wall. Within the submucosa there was pancreatic tissue which largely replaced the Brunner glands in this area. These pancreatic cells were mostly of acinar type and typical in arrangement. There were also a few islets of the Langerhans type. The connective tissue stroma between the pancreatic lobules was fairly prominent.

Case 20.—B. P., a man aged 60, was admitted to the hospital with the complaint of abdominal pain of three weeks' duration. Two weeks before admission

he began to suffer from loss of appetite and a continuous dull ache in the right lower quadrant of the abdomen. Physical examination revealed a slightly emaciated, icteric man. The liver was enlarged, and there was tenderness in the epigastric region. Otherwise the examination gave negative results.

Operation.—An exploratory laparotomy was performed. Thin bloody fluid was found within the abdominal cavity. Biopsy of hepatic tissue showed carcinoma without a demonstrable primary focus. The patient died on the sixth postoperative day.

Gross Pathologic Description.—Autopsy showed a carcinoma of the kidney with metastases to the lungs and liver. In the first part of the jejunum beneath the peritoneum there was a firm, white to pinkish-gray plaque surrounding about one third of the circumference of the intestine. This plaque measured 3 by 2 cm. and was 0.5 cm. in thickness. On incision it appeared to lie between the mucosa and the muscularis. It was lobular and had the general appearance of normal pancreatic tissue.

Microscopic Examination.—The sections showed inclusion of pancreatic tissue in the wall of the jejunum. This aberrant tissue lay in the submucosa and also between the muscle bundles. The inner surface of the intestine was entirely covered by mucosa, and the external surface was completely covered by a layer of muscle and serosa. The pancreatic substance consisted of groups of acinar cells arranged in lobules and reproducing essentially the structure of normal pancreatic tissue. No islets of Langerhans were seen. There were a few intermixed ducts. The larger ones were lined by tall columnar epithelium; the smaller ones showed a cuboidal type of epithelium. No ducts were seen emptying into the intestinal lumen. The stroma was prominent in some areas, and a few lymphocytes were found in this supporting tissue. There was no evidence of ulceration or inflammatory reaction in the overlying mucosa.

Case 21.—E. N., a woman aged 65, came to the hospital on Oct. 23, 1929, because of weakness and loss of weight of several years' duration. For the preceding three months the patient's appetite had been poor. There had been repeated attacks of vomiting, an attack occurring after almost every meal.

The results of physical examination were not remarkable except for consolidation in the upper lobe of the right lung and evidence of loss of weight. Laboratory findings showed the number of red cells to be 4,200,000, the hemoglobin, 75 per cent, and the number of white cells, 30,000. The urine was normal. Examination of the stool disclosed a 4+ reaction to the benzidine and guaiac tests.

The patient became gradually weaker and more cyanotic. Death occurred on Oct. 28, 1929.

Gross Pathologic Description.—There was evidence of bilateral lobar pneumonia which was the immediate cause of death. On the anterior wall of the first portion of the duodenum, 3 cm. distal to the pyloric ring, there was an elevated, white nodular mass, measuring 1.5 cm. in diameter and 7 mm. in thickness. This was firm but not hard. Its internal surface supported a fibrinous blood clot; when this was removed an indurated ulcer 1 cm. in diameter with well defined edges was seen. The surface ulceration was the site of the intestinal bleeding. There was changed blood along the intestinal tract below this site. The other results of the autopsy were of secondary importance.

Microscopic Examination.—Section of the duodenal ulcer showed aberrant pancreatic tissue which was not continuous with the normal pancreas. This aberrant tissue completely replaced the intestinal glands and the Brunner glands and pene-

trated the entire duodenal wall to present on the serosal surface of the duodenum (fig. 6). The circular and longitudinal muscle of the duodenum coursed in isolated strands through the pancreatic tissue. This pancreatic substance was composed entirely of acinar cells in normal lobulations. Small ducts with cuboidal epithelium were scattered through the tissue. No islets of the Langerhans type were present. Through the pancreatic substance there was a mild infiltration of lymphocytes, of polymorphonuclear leukocytes and especially of endothelial leukocytes. This leukocytic reaction was almost entirely limited to the tissue just below the surface facing the intestinal lumen. Toward the intestinal lumen there was a hemorrhagic necrosis of acinar tissue, and on the surface of the pancreatic tissue there was a fibrinohemorrhagic exudate. A small artery was found eroded in the base of the ulceration. This contained an unorganized fibrinous thrombus and was obviously the site of the intestinal bleeding. Chronicity of the ulcerative process was indicated by a moderate fibroblastic proliferation and fibrosis between the acini just beneath the surface of the lumen.

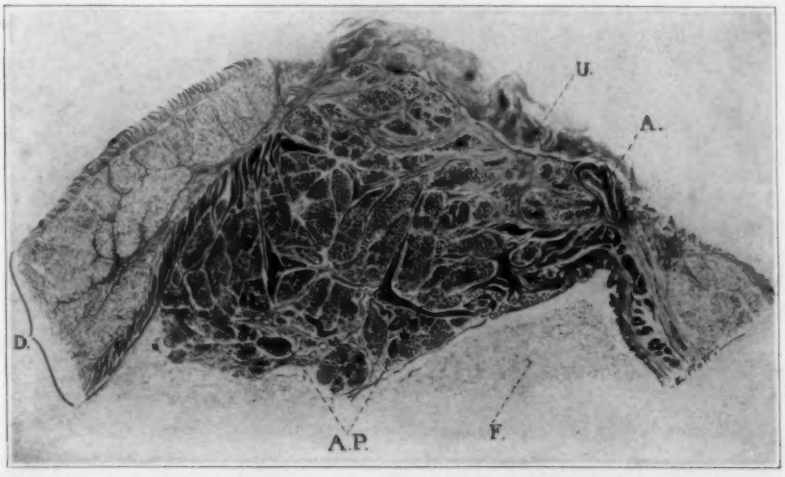

Fig. 6 (case 21).—Camera lucida drawing from microscopic section (× 4) showing aberrant pancreatic tissue in the wall of the duodenum. The duodenal mucosa is absent over the pancreatic tissue, and there is an ulceration in this area. *D.* indicates the duodenal wall; *A.P.*, aberrant pancreatic tissue; *F.*, fat; *U.*, ulceration on the internal surface, and *A.*, an eroded artery from which hemorrhage occurred.

Case 22.—D. B., a woman aged 66 years, entered the hospital on Sept. 28, 1932, complaining of sour eructations and indigestion of fifteen years' duration. At the onset of the illness there was epigastric pain which occurred twenty minutes after each meal. Roentgen studies of the intestinal tract at that time were said to have given negative results. Recurrence of these symptoms ten years later was followed by a remission. During the past five years the indigestion had been present intermittently. One year before admission the patient had suffered from severe sour eructations after meals. On Sept. 7, 1932, she was admitted because of severe arthritic pains in the left wrist. Roentgen studies of the gastro-intestinal tract showed slight dilatation of the stomach with a residue of from 40 to 50 per cent.

There was a constant filling defect just proximal to the pylorus (fig. 7). The stomach wall, however, was flexible in this area. The changes were interpreted as due to an inflammatory lesion causing partial obstruction of the pylorus.

Physical Examination.—This showed a well developed but poorly nourished woman in good general condition. The results of the examination were essentially normal.

Laboratory Examination.—Routine studies of the blood and urine gave normal results. Gastric analysis showed free hydrochloric acid equivalent to 50 cc., and total acidity equivalent to 79 cc., of tenth-normal sodium hydroxide. The Wassermann and Hinton reactions of the blood were negative.

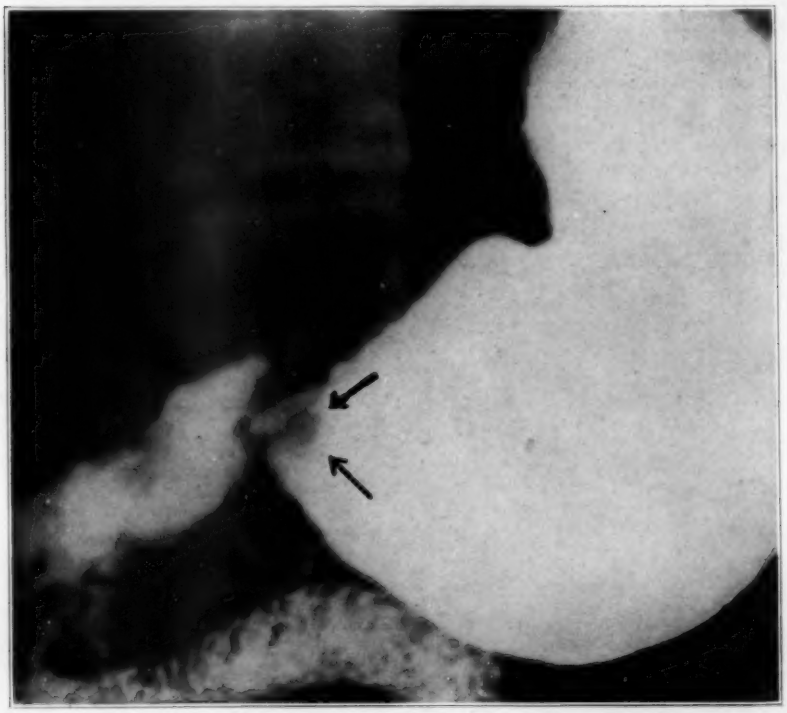

Fig. 7 (case 22).—Roentgenogram showing a filling defect in the gastric antrum produced by a pancreatic nodule projecting in from the posterior wall of the stomach (compare with figure 8).

Operation.—On September 29 an abdominal exploration was performed by Dr. Elliott C. Cutler. Palpation of the antral end of the stomach revealed a mass 1 cm. in diameter in the posterior wall of the stomach in the prepyloric area. This projected into the lumen at this site so as to partially obstruct the pylorus. The antral end of the stomach and a part of the duodenum were resected. Reanastomosis was performed by Horsley's method.

The postoperative course was uneventful, and the patient was discharged fifteen days later.

Gross Pathologic Description.—No area of ulceration was seen in the gastric or duodenal mucosa. Proximal to the pyloric sphincter there was a small, round,

nodular whitish mass, 1 cm. in diameter. This nodule projected well into the lumen of the gastric antrum (fig. 8). The mucosa covering this nodule was congested. When the mass was cut through it was found to contain a small amount of clear mucus. A small ductlike orifice was found in the mucosa of the duodenum just beyond the pyloric ring. This duct lay at the edge of the nodular mass described and admitted a fine probe for a distance of about 2 mm. in the direction of the nodule. From this orifice a small amount of fluid could be expressed.

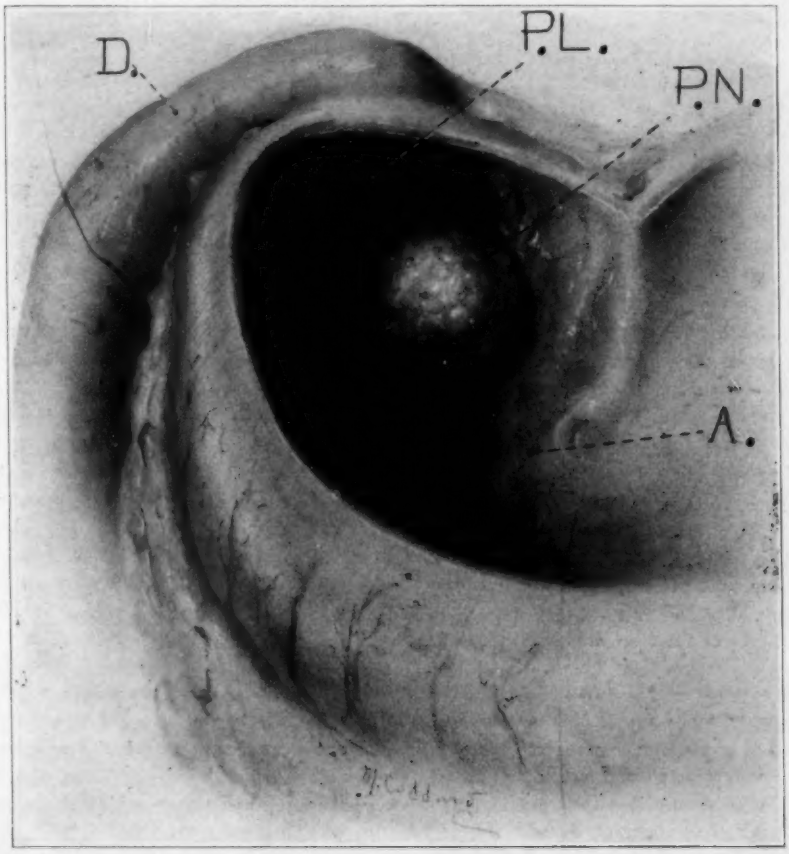

Fig. 8 (case 22).—Drawing illustrating a nodule of pancreatic tissue projecting into the stomach so as to obstruct the pyloric lumen. *A.* indicates the antrum of the stomach; *D.*, the duodenum; *P.L.*, the pyloric lumen, and *P.N.*, the pancreatic nodule.

Microscopic Examination.—Serial sections were made of the lesion. The nodule situated in the submucosa consisted of a number of different structures which fused into a single anomalous mass. The nodule was composed mostly of numerous secretory glands and acini which were similar in appearance to Brunner's glands. These drained into ducts which in turn emptied into the intestinal lumen. These ducts were lined by tall columnar epithelium. Intermixed with these glandular

elements were islands of pancreatic acinar tissue, varying from 0.5 to 1.5 mm. in their greatest dimensions. These cells contained secretory granules. The small ducts lined with cuboidal epithelium which drained this acinar tissue emptied in turn into the previously described larger ducts. No islets of the Langerhans type were present. There was no active inflammatory process in the aberrant pancreatic tissue. Overlying the ducts, at a point just proximal to their entry into the bowel, there was a tiny ulcer in the gastric mucosa. This was wholly superficial to the muscularis mucosae and measured about 0.5 mm. in diameter. Its base was formed by a thin layer of fibrin and polymorphonuclear leukocytes which replaced the epithelium.

CASE 23.—J. R., a man aged 69, was admitted to the hospital on Aug. 26, 1931. He complained of constipation of four months' duration. There was a history of considerable loss of weight in the year before admission. Physical examination showed a somewhat emaciated, elderly man with mild abdominal distention. The remainder of the examination disclosed no remarkable features. An enema with barium revealed an irregularity in the first portion of the sigmoid colon, and a diagnosis of carcinoma of the sigmoid colon was made. A cecostomy was established on August 26, and a Mikulicz resection of the sigmoid colon was performed on September 1. Pulmonary complications developed after the operation, and the patient died on September 8.

Gross Pathologic Description.—On the anterior surface of the first portion of the duodenum there were seven firm white nodules, varying from 1 to 9 mm. in diameter. At the time of autopsy these were thought to represent implantations from the colonic carcinoma. There was no ulceration of the mucosa on the internal aspect of the duodenum.

Microscopic Examination.—The largest nodule was 9 mm. in diameter and 4 mm. in maximum thickness. It partially replaced the submucosa and the muscularis. In a few places it protruded up through the muscularis mucosae, but it was entirely covered by duodenal epithelium. In a few places it extended through the muscularis. It was entirely covered on its external surface by serosa of the duodenum. This nodule consisted largely of ductal elements of varying size. Some of these were lined with cuboidal epithelium; others were lined with a columnar type of epithelium. In many areas there were numerous small ductules. There were a few small islands of cells of the pancreatic acini type, but these elements were much less prominent than the duct formations. There were no cells of the Langerhans islet type. This aberrant pancreatic tissue had a moderate stroma, scattered through which there were occasional lymphocytes. There was no evidence of an active inflammatory process. Bundles of duodenal musculature coursed through this aberrant tissue. The remaining nodules were all from 1 to 3 mm. in diameter. They were situated external to the duodenal muscularis but were all covered by the serosa. These smaller structures all showed essentially the same histologic structure as did the larger nodule.

CASE 24.—E. L., a woman aged 82, entered the hospital on May 21, 1934, with the complaint of cough, fever and pain in the chest. A typical bronchial pneumonia developed, and the patient died on the fourth day of hospitalization.

The past history revealed that the patient had had some sour eructations four years previously. She was admitted to the hospital at that time, and roentgen studies showed no evidence of abnormality of the stomach or duodenal cap. Examination of the stool at that time showed 4+ reactions to benzidine and guaiac tests. These reactions were not obtained on subsequent examination.

Pathologic Description.—On the anterior surface of the second portion of the duodenum there was a projecting, finger-like diverticulum, 3 cm. in length and 1.5 cm. in diameter. Over the distal three fourths of the diverticular surface there was a caplike thickening beneath the serosa which varied from 1 to 4 mm. in thickness. This was finely lobulated and pinkish gray and grossly suggested a thin sheet of aberrant pancreatic tissue distributed over the surface of the diverticulum. The inner surface of the diverticulum showed no ulceration or scarring of the mucosa.

Microscopic Examination.—The aberrant pancreatic tissue was found in the submucosa, scattered through the muscularis which it divided into separated bundles, and in the adjacent serosal fat (fig. 9). The major part of this substance duplicated closely the architecture of normal pancreas. There was a normal arrangement of acinar cells into primary and secondary lobules. The islets of

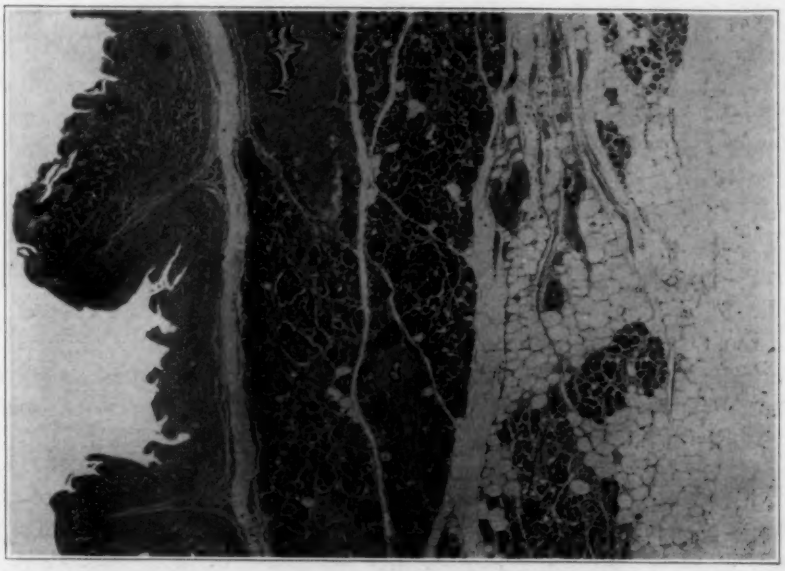

Fig. 9 (case 24).—Photomicrograph (× 15) of aberrant pancreatic tissue occurring in the wall of a duodenal diverticulum.

Langerhans were numerous and large. The stroma of most of the tissue had about the same prominence as that observed in normal pancreas, but in a few areas, particularly toward the inner parts of this tissue, there were broad zones of dense stroma in which there were many dilated ducts. Some of these ducts apparently emptied into the lumen of the diverticulum. The mucosa was duodenal in type, but the Brunner glands were not numerous. There was no ulceration or scarring of the mucosa, but lymphoid elements in the tunica propria were quite prominent.

COMMENT

Twenty-four cases in which aberrant pancreatic tissue was discovered at examination of autopsy material or of surgical pathologic specimens are reported in this series. Twelve of the patients were males, and

twelve were females. The youngest patient was 8 days old and the oldest was 82. The majority of these anomalies were found at autopsy; in only five cases was the aberrant tissue identified during the course of an abdominal operation. In two of the cases the aberrant pancreatic tissue was located in the wall of the stomach, and in each of these a partial resection of the stomach was performed because it was thought that the nodular structure was carcinomatous. The pyloric ring was the site of the pancreatic tissue in one patient. The anomaly was found in the duodenum in ten cases; in one of these the pancreatic substance was located in the wall of a duodenal diverticulum. Four of the nodules occurred in the jejunum, and one in the ileal wall. In the remaining six cases the pancreatic tissue occurred in a Meckel diverticulum.

The masses of aberrant pancreatic tissue varied in size, as is shown by the summary in the table. The nodules were often flattened and were from 5 to 8 mm. in diameter. The largest single mass was 3 cm. long, 2 cm. wide and 0.5 cm. thick. Another specimen was 1.5 cm. in diameter and 7 mm. in thickness. A third nodule was 1 cm. in diameter. In another case an entire duodenal diverticulum, 3 cm. in length and 1.5 cm. in diameter, was capped by aberrant pancreatic tissue from 2 to 5 mm. in thickness.

The pancreatic tissue was present in various portions of the intestinal wall. Figure 1 shows such a nodule lying in the submucosa covered on the inner surface by mucosa and externally by muscularis. Figures 2, 3 and 9 show islands of pancreatic tissue occurring in intestinal diverticula. Histologically the aberrant substance, as a rule, closely resembled normal pancreatic tissue, showing normal-appearing acinar lobules, stroma, ducts and islets of Langerhans. In fifteen of the specimens there were no islets in the sections studied; in the remaining nine cases, typical islets were identified (fig. 4). In most of the cases in which islets were not seen the microscopic structures were similar to those of normal pancreatic tissue with this one exception. A few specimens showed a great overgrowth of ductal elements as compared with the acinar structures (fig. 5). The presence of zymogen granules in acinar cells indicated that this aberrant tissue was usually functioning.

The aberrant pancreatic tissue was the site of a pathologic lesion in four of the twenty-four cases. In one of these (case 22) operation was performed because of a fifteen year history of sour eructations and indigestion with epigastric pain after meals. Roentgenograms had disclosed a partial obstruction of the pylorus (fig. 7). At the time of operation the cause of obstruction proved to be aberrant pancreatic tissue which projected into the gastric lumen and obstructed the outlet of the stomach (fig. 8). Resection of this mass has effected complete relief of symptoms. In the second case (case 21) there had been repeated attacks of vomiting for several months with an associated loss of weight

and the onset of general weakness. Examination of the stools by means of benzidine and guaiac tests had shown the presence of blood. Pneumonia developed, and the case terminated fatally. At autopsy a bleeding ulcer was found in the first portion of the duodenum. On microscopic examination, this proved to be ulcerated aberrant pancreatic tissue in which there was a large eroded artery that had ruptured because of the ulcerative process in the pancreatic substance (fig. 6). The duodenal ulceration was obviously the important lesion in this case and was the cause of the chronic illness. In the third case (case 16) there was a gastric ulcer in the inflammatory mass of which were found many small "nubbins" of pancreatic tissue. Since the removal of the lesion there have been no gastric symptoms. In the fourth case (case 7) the specimen proved to be a bleeding ulcer of the duodenum; it was found at autopsy; its existence had not been suspected during the patient's life.

From the study of this series of cases there is little to support any one theory as to the genesis of aberrant pancreatic tissue, but the material lends strong support to the belief that such a nodule of pancreatic substance is antenatal in origin. It seems most probable that the occurrence of aberrant pancreatic tissue is a congenital abnormality which arises either as an anomalous anlage or as an inclusion of primitive pancreatic tissue in a portion of the foregut or its derivatives. Although King and MacCallum expressed the belief that pancreatic acinar tissue may arise from the gastric epithelium under the influence of a chronic inflammatory reaction, we are strongly opposed to this theory as the proper etiologic explanation in the majority of cases. In support of their contention, King and MacCallum called attention to the fact that all their patients were elderly persons; they assumed from this fact that pancreatic tissue did not appear until in adult life, when ulceration or inflammatory change in the gastric epithelium had occurred. Our observations contradict this view, for thirteen of our patients were under 12 years of age and eight of these were in the first year of life. Furthermore, in the majority of our cases there was no evidence of an active inflammatory process or of old scarring in the pancreatic tissue to indicate that inflammatory lesions had instigated a metaplasia and the formation of pancreatic tissue. The view that aberrant pancreatic tissue is an atavistic phenomenon is also not acceptable, for there is no record of pancreatic tissue having this wide dissemination in a human embryo at any stage in its development. The finding of such an embryologic stage would be necessary if the phylogenetic theory were the proper explanation. We are therefore of the opinion that these aberrant masses of pancreatic tissue represent congenital anomalies, that they are the result of aberrations from the normal development and do not represent a stage normally present in fetal growth.

SUMMARY

Approximately two hundred cases in which aberrant pancreatic tissue was found have been recorded in the literature. In the majority of these the tissue occurred in the gastro-intestinal tract. This report adds twenty-four other cases in which aberrant pancreatic tissue was found in various locations in the wall of the alimentary canal. The distribution was as follows: In three instances the tissue was found in the stomach or pylorus; in ten, in the duodenum (in one in a duodenal diverticulum); in four, in the jejunum; in one, in the ileum, and in six in a Meckel diverticulum. These structures contained ductal and acinar elements the histologic structure of which closely resembled that of normal pancreatic tissue. In fifteen specimens there were no islets of Langerhans in the sections studied, but in the other nine cases there were typical islets. The age of the patients in whom the anomalous tissue was found varied from 8 days to 82 years. The cases occurred in equal numbers in males and in females. The presence of this aberrant pancreatic tissue in the gastro-intestinal tract probably represents a congenital anomaly in most, if not in all, instances.

Four of these twenty-four cases had important pathologic significance. In one of these the nodule caused pyloric obstruction, and in the other three it was the site of ulceration in the stomach or duodenum.

Such a nodule in the wall of the gastro-intestinal tract has been mistaken for carcinoma. The gross appearance of the tissue should indicate that it is pancreatic in type and should obviate the danger of unnecessary removal when it is not the cause of intestinal obstruction or the site of an important pathologic lesion.

ULCERATIVE COLITIS

STUDY OF BACTERIA IN THE ISOLATED COLONS OF THREE PATIENTS BY CULTURES AND BY INOCULATION OF MONKEYS

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Ileostomies are occasionally made in patients with severe ulcerative colitis for the purpose of putting the colon at rest. In some of these patients, the colon does not heal following operation and rectal discharges of blood-streaked purulent material may persist for years.[1] A study of the kinds of bacteria inhabiting the isolated diseased colon, in the absence of organisms maintained by a fecal current, should extend knowledge of the bacteriology of ulcerative colitis.

In this investigation a bacteriologic study was made of the contents of the isolated colon in three patients with ulcerative colitis, in each of whom an ileostomy had been performed. These patients were as follows: (1) Mrs. N., aged 21 years, in whom an ileostomy was performed on April 21, 1933; (2) Mrs. P., aged 29 years, in whom an ileostomy was performed on Oct. 18, 1933, and (3) Mrs. S., aged 47 years, in whom an ileostomy was performed on Sept. 22, 1931. In an attempt to evaluate the significance of certain organisms isolated from these patients, some experiments were carried out with monkeys (Macacus rhesus), rabbits and guinea-pigs.

The specimens used in this study were usually obtained by passing a sterilized soft rubber urethral French catheter into the rectum and aspirating material through this catheter into a sterile syringe. In many cases it was necessary to introduce a few cubic centimeters of sterile saline solution into the bowel in order to obtain an adequate sample. Some cultures were taken from the lesions on a swab at the time a proctoscopic examination was made. The specimens were always mucopurulent and somewhat blood-tinged.

The material was examined for amebas, and smears were made on slides and stained with Wright's stain in order to study the types of cells present. Gentian violet stains were also made to reveal any spirochetes or fusiform bacilli. Finally a Gram stain was made to differentiate the types of bacteria. No amebas, intes-

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1. Bargen, J. Arnold; Brown, Philip W., and Rankin, Fred W.: Surg., Gynec. & Obst. **60**:196, 1932.

tinal spirochetes or fusiform bacilli were ever found. No unusual cell types were present in the bloody mucopurulent specimens.

A few specimens, taken by swabbing the lesions at proctoscopic examination, were put into dextrose brain broth, and after six hours' incubation at 37 C. in this medium the growths were streaked on blood agar plates. Gram-positive diplococci were sometimes demonstrated but were frequently absent.

Eosin methylene blue plates were always streaked with the original specimen for isolation of dysentery organisms, but none were ever found.

Decimal dilutions were made of the specimens in saline dilution blanks, and 1 cc. portions of the various dilutions were put into dextrose beef heart medium (1 per cent dextrose added to Robertson's [2] beef heart meat medium) and into lactose broth fermentation tubes. The former was an excellent medium for the growth of streptococci, Bacteroides (anaerobic gram-negative and gram-positive nonsporulating rods), Bacillus acidophilus and many other types of organisms. This medium was so prepared that the supernatant fluid above the ground meat was clear; growth was indicated by turbidity.

Blood agar plates (10 per cent sheep blood in veal infusion agar base) were streaked directly with the specimens. Some were incubated aerobically and others anaerobically. The anaerobic blood agar plates were placed in large pyrex vacuum desiccators, and the pressure was reduced to the vapor tension of water. One atmosphere of carbon dioxide was then admitted, and the jar was exhausted to the vapor tension of water, placed in the incubator and incubated at 37 C. for four days. A solution of pyrogallic acid and sodium carbonate was kept in the bottom of the anaerobic jars to remove traces of the oxygen which was slowly given up from the blood in the medium.

With patient 1, specimens were collected from the colon at intervals of two weeks for a period of two months following the operation. After that time monthly examinations were made. With the second patient, fifteen specimens were collected at weekly intervals after the operation. With the third patient, only two specimens were taken, three months apart and two and one-half years following the operation. The organisms isolated from the first two patients immediately following the operation were essentially the same as those commonly encountered in fecal examinations. There was, however, a marked change in the type of organisms predominating in the bowel. During this transition from one type of flora to another, an organism of the genus bacteroides was recovered from the highest dilutions of the specimens put into beef heart dextrose medium. This organism was an anaerobic, small, gram-negative, nonsporulating rod which formed acid in dextrose, sucrose, lactose and glycogen, but failed to ferment glycerol, mannitol, sorbitol, arabinose, salicin and rhamnose. It did not liquefy gelatin or form indol in tryptophan broth. Strains with similar reactions were recovered from the isolated normal colons of two monkeys.

The flora of the isolated colons of patients 1 and 2 ultimately resembled that found in the colon of the third patient, in whom ileostomy had been performed two and one half years before, the colon having been undisturbed during that time. This type of flora was demonstrated

2. Robertson, M.: J. Path. & Bact. **20**:327, 1915-1916.

fifteen months after ileostomy in patient 1 and ten weeks after ileostomy in patient 2. The length of time required for the flora of patient 1 to become similar to that of the others was due to the fact that organisms of the Proteus type appeared and persisted in large numbers in the colon following the operation, overgrowing other types on artificial mediums. After fifteen months, however, these organisms had disappeared, and the flora of this patient resembled that of the other two.

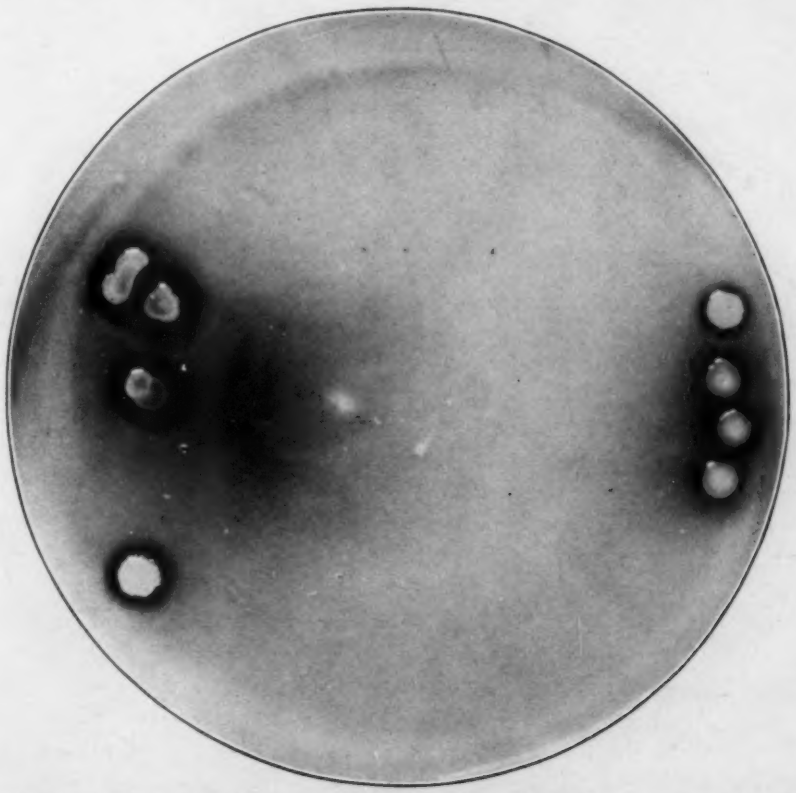

Fig. 1.—Blood agar plate streaked with specimen from Mrs. P., Dec. 22, 1933, and incubated aerobically for four days at 37 C.

At this stage few colon bacilli were present, and the flora was predominantly anaerobic. Few colonies appeared on aerobic blood agar plates, but thousands of colonies were present on similar plates streaked with the same amount of material and incubated anaerobically. Two types of bacteria growing on anaerobic blood agar plates were common to the three patients and greatly outnumbered all other organisms. They were (1) the predominant organism, to be described later, and (2) a strictly anaerobic nonhemolytic organism which formed a pinpoint-size colony and which proved to be a gram-negative streptococcus. The

latter was not pathogenic for guinea-pigs when injected subcutaneously (figs. 1 and 2).

The colonies of the predominant organism were round, grayish and raised, measuring, when well isolated, from 0.5 to 1 mm. in diameter (fig. 3). When the plates were removed from the desiccators they had a putrid odor resembling somewhat that of butyric acid. There was no zone of hemolysis about these colonies when first removed from the

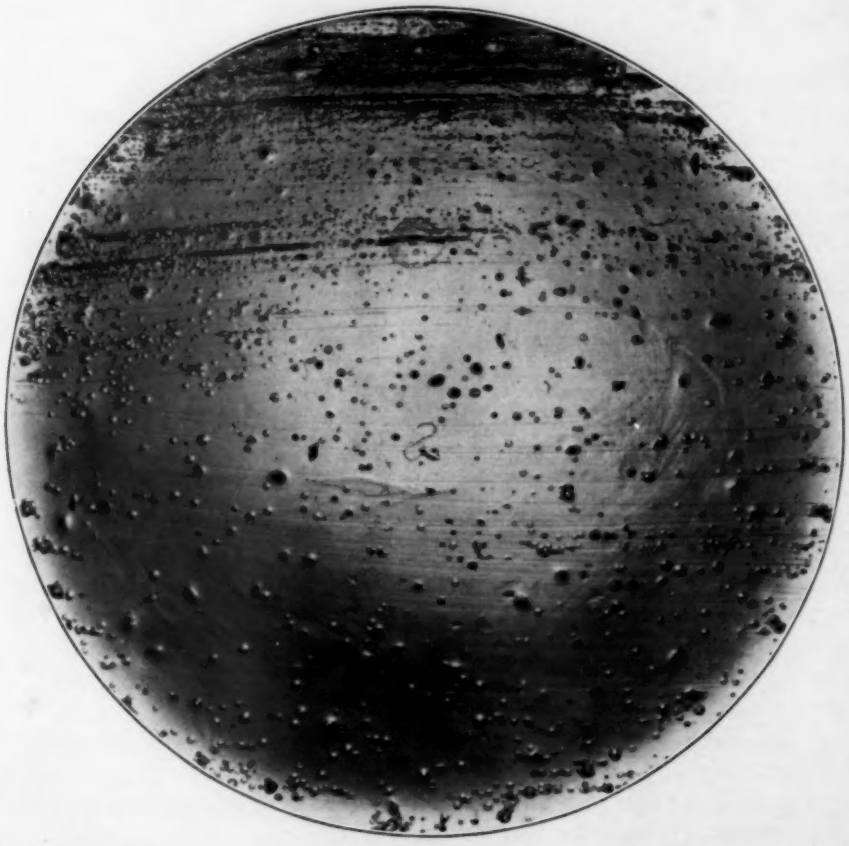

Fig. 2.—Blood agar plate streaked with specimen from Mrs. P., Dec. 22, 1933, and incubated anaerobically for four days at 37 C.

anaerobic environment, but as oxygen was taken up by the hemoglobin in the blood a greenish zone of hemolysis appeared around them.

When picked from the plates the colonies had a tendency to stick together. In smears they appeared as gram-negative rods and filaments (shown in figs. 4 and 5). Many of the cells stained faintly and appeared as "ghost" forms. Often a long filament would stain irregularly, and bulges would appear in portions of it. The organisms occasionally grew anaerobically, but never aerobically, when transferred to blood agar

slants. After a strain was started from a single colony it could be readily maintained by transferring a large amount of the growth to blood agar slants and incubating anaerobically. The organisms did not grow in veal infusion mediums or in dextrose beef heart or dextrose brain broth. Good growth occurred in dextrose cystine agar, recommended by Shaw.[3] If another carbohydrate was substituted for dextrose in the cystine agar, growth often did not appear. The organism

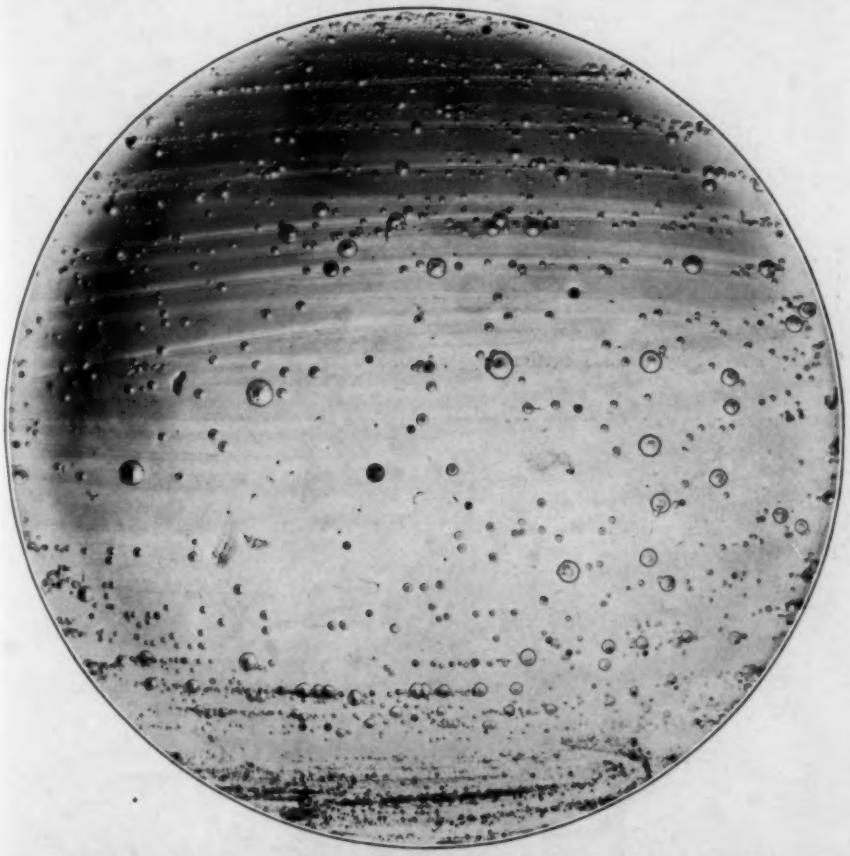

Fig. 3.—Colonies on blood agar plate streaked with specimen from Mrs. S. (taken May 12, 1934) and incubated four days in an anaerobic jar at 37 C. The largest colonies are those of Proteus. The predominant colony is surrounded by a zone of green hemolysis, which does not appear in the photograph. A few tiny pinpoint-size colonies are present, which in smears showed gram-negative streptococci. Some areas may be seen where colonies were scraped off for staining.

also grew in sheep serum (20 per cent) dextrose veal infusion broth under anaerobic conditions. When dextrose was replaced by another carbohydrate in the serum broth, growth frequently did not occur. The

3. Shaw, Frederick W.: Zentralbl. f. Bakt. (Abt. 1) **129**:132, 1933.

Fig. 4.—Strain 11 on anaerobic blood agar plate incubated four days at 37 C. Colony stained by Gram's method; × 2,000.

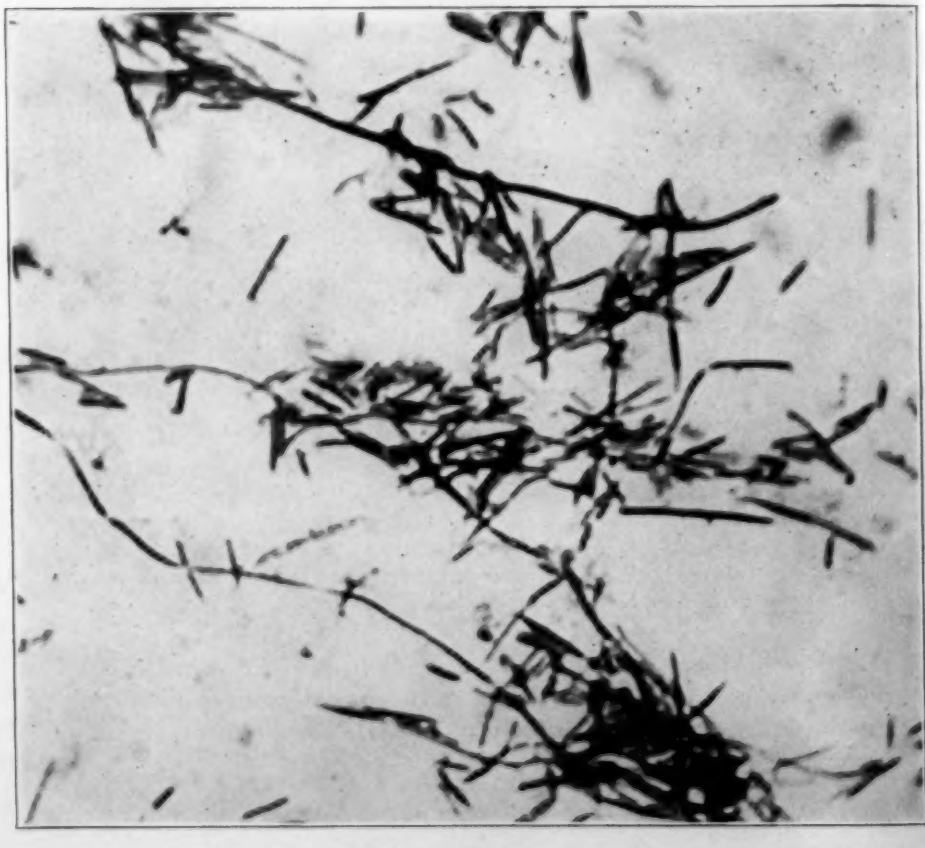

Fig. 5.—Strain 40 on anaerobic blood agar plate incubated four days at 37 C. Colony stained by Gram's method; × 2,725.

biochemical reactions were tested after fourteen days' incubation of the tubes in an anaerobic jar. Acid was produced in dextrose medium, but lactose, sucrose, salicin, inulin, mannite and glycerin were not broken down. Milk was unchanged. The strain isolated from patient 1 liquefied gelatin in one of two tests with gelatin serum medium, but failed to do so in two tests with gelatin cystine medium. The other strains, with the exception of strain 39, did not liquefy gelatin.

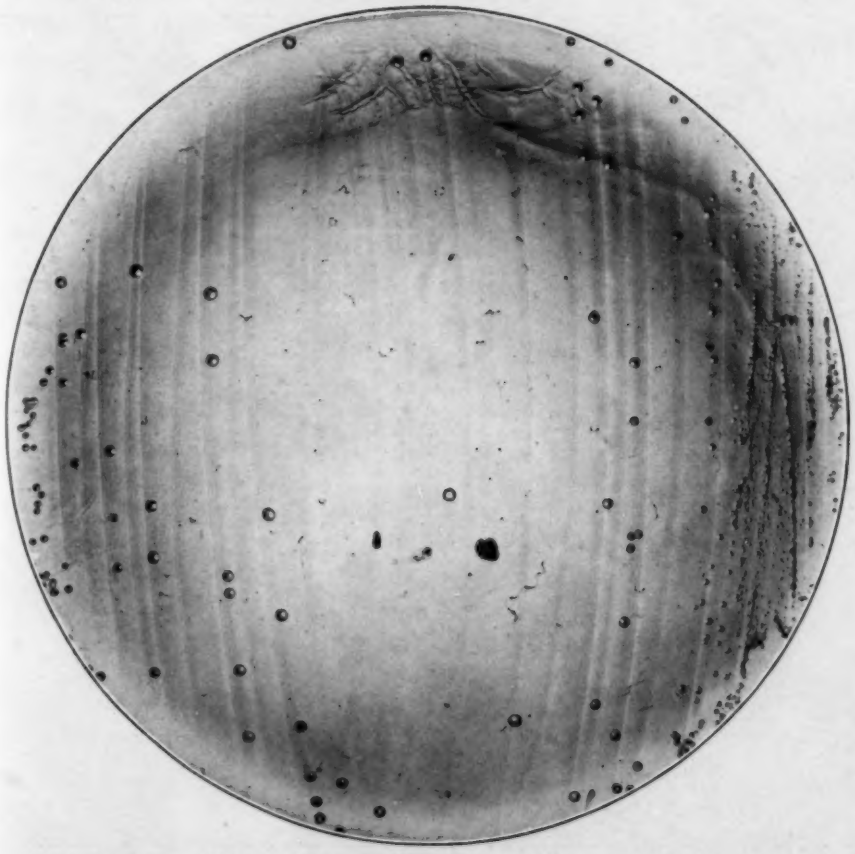

Fig. 6.—Anaerobic blood agar plate streaked with pus obtained from an abscess in a rabbit eight days after subcutaneous injection of strain 11. The plate had been incubated four days at 37 C.

Four strains were studied in animals. These were: strain 40 from patient 1, strain 11 from patient 2, strain 38 from patient 3 and strain 39 from monkey 6, which died of bacillary dysentery (Flexner type).

Rabbits inoculated subcutaneously with the growth from anaerobic blood agar plates heavily inoculated with these strains acquired abscesses at the sites of injection. Pure cultures of the organisms were obtained when anaerobic blood agar plates were streaked with the thick creamy

pus found in the abscesses (fig. 6). Gram-negative rods were found in the stained pus (fig. 7). No filaments were observed. The abscesses either drained spontaneously or were absorbed. No lesions other than the local abscesses followed the subcutaneous injection of these cultures into rabbits. Guinea-pigs inoculated subcutaneously in the groin with strain 11 and with an anaerobic gram-negative streptococcus isolated from the colon specimen of patient 2 on Jan. 19, 1934 did not

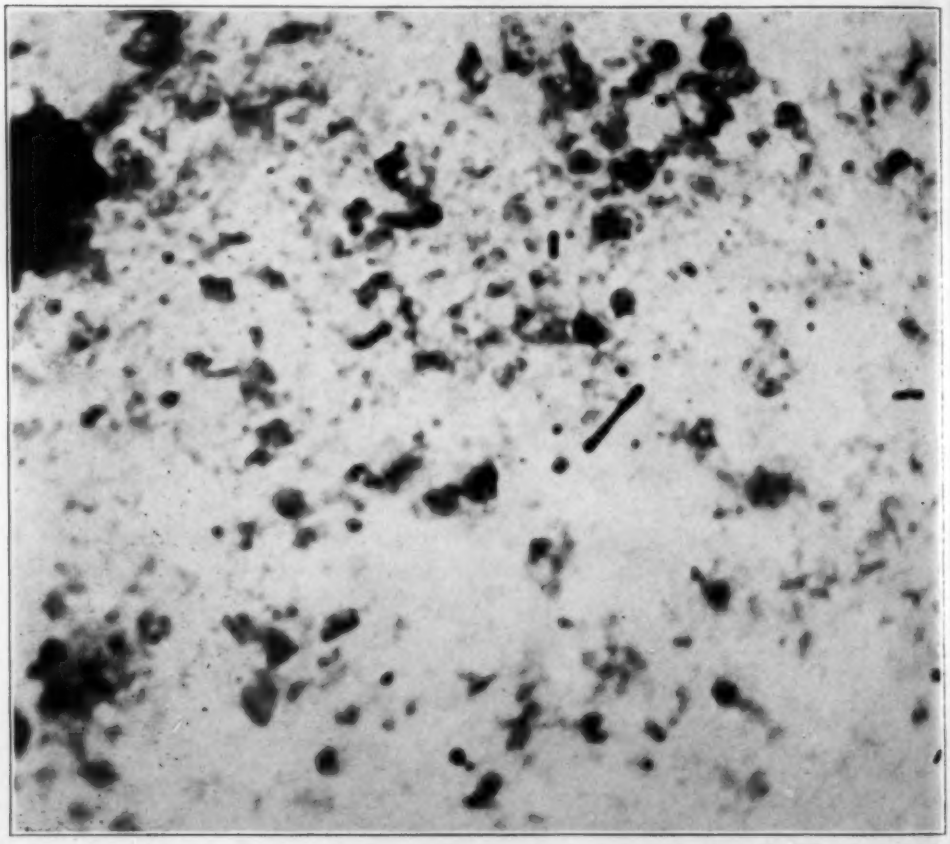

Fig. 7.—Gram stain of a smear of pus aspirated from an abscess in a rabbit fifteen days after subcutaneous injection of strain 38; × 2,725.

present abscesses or appear ill. Mixtures of these two organisms also failed to produce symptoms when similarly administered.

These filamentous gram-negative anaerobic organisms were not found in the stools of four healthy monkeys, although eight different examinations were made. However, from one monkey (6), which died after contracting a spontaneous bacillary dysentery (Flexner type), a similar organism was isolated on an anaerobic blood agar plate streaked

with mucopurulent material taken from the descending colon. At necropsy on this animal no gross pathologic change was observed except in the colon. The serosa was injected throughout and that in the descending colon showed small petechial hemorrhages. When the large bowel was opened, the mucosa appeared grossly edematous, was covered with mucopurulent material and contained numerous pinhead-sized superficial ulcerations. This strain resembled very closely the others obtained from the diseased colons of patients 1, 2 and 3, and was designated as strain 39. A Flexner dysentery organism was cultured from the same specimen.

A monkey (C P) with an isolated cecum and ascending colon was operated on, May 7, 1934, at which time the isolated bowel was resected. After the operation there was considerable drainage from the wound. About ten days following the operation the animal presented a profuse watery diarrhea which persisted for two or three weeks. On May 22, a proctoscopic examination was made, at which time the mucosa of the lower part of the colon was found to be very hyperemic. Through the proctoscope a swab was rubbed over the mucosal surface, and blood agar and eosin methylene blue agar plates were streaked. Some of the blood agar plates were incubated anaerobically and others aerobically. Numerous colonies resembling those of Bacterium coli grew on the eosin methylene blue plates and aerobic blood agar plates. On the anaerobic blood agar plates numerous green hemolytic colonies appeared which were indistinguishable morphologically from culture 39 or strains 11, 38 and 40. One colony was picked and put on two blood agar slants. One was incubated aerobically and the other anaerobically. Neither culture grew, which conforms with previous experience. Complement-fixation tests were made on the serum of this monkey.

Rectal mucosa was removed from each of two monkeys. One of these animals (1) had been fed culture 11 on March 20, 1934, and a similar organism was isolated from the bowel two days later. On four subsequent weekly examinations no typical green hemolytic colonies were found. A spontaneous prolapse of the rectum occurred in this monkey following a proctoscopic examination on April 23. When prolapse of the rectum was produced, an area of mucosa about a centimeter in diameter was removed with forceps and a scalpel. Three days later another proctoscopic examination was made, and prolapse again produced. A thick grayish necrotic membrane covered the previously denuded area. Part of this membrane was dissected off and cultured immediately. Numerous well isolated green hemolytic colonies developed on anaerobic blood agar plates. There were two types of these colonies: One type resembled strain 39 in every detail. The other type of colony was flat, smooth and somewhat larger than that resembling strain 39 and

was made up of uniform long slender gram-negative rods which were pointed at the ends. Both types of colony were anaerobic. Portions of rectal mucosa were removed from this animal three different times during a period of three weeks. Each time the necrotic membrane over the lesion was cultured, and each time the same types of colonies grew out on anaerobic blood agar plates. Eighteen days after the first removal of the mucosa, prolapse of the rectum was produced, and the growth from six anaerobic blood plates of strain 38 was taken up in sterile saline solution and injected submucosally into a portion of the rectum which had not previously been denuded of mucosa. The bowel was made to prolapse and was examined three days later, and no ulcerations or lesions were seen about the site of injection. Complement-fixation tests were made with the serum of this monkey.

The second monkey (2) was anesthetized with pentobarbital sodium, and a low midline incision was made above the symphysis pubis. The rectum was invaginated over a gloved finger and a portion forced out through the anal sphincter. A second operator then denuded the mucosa of the portion of bowel over the finger. When the bowel was replaced no perforation was seen. Cultures were taken through a proctoscope two days later. The anaerobic blood agar plates were overgrown with a spreading Proteus-like organism. However, one green colony was seen in mixture with the Proteus-like spreader. This colony, when picked and stained, appeared to be made up of long gram-negative rods and filaments and corresponded to strain 39 and the other similar strains, 11, 38 and 40. Complement-fixation tests were also made with the serum of this monkey.

Two monkeys were fed culture 11 by stomach tube; one received a saline suspension of the growth from three anaerobic blood agar plates, and the other the growth from four similar plates. No symptoms developed in these animals. From a colon specimen taken forty-eight hours after feeding the organism to one of the monkeys (1) an isolated green colony developed on an anaerobic blood agar plate. This colony, when stained, resembled the type of organism which had been fed this animal. A Proteus-like organism overgrew the anaerobic blood plate culture from a specimen taken forty-eight hours after feeding the other monkey (3).

COMPLEMENT-FIXATION TESTS

Strains 11, 38, 39 and 40, when grown anaerobically on blood agar plates, were found to be unsuitable as antigens for agglutination tests, since the growth removed from these plates was clumped. The antigens in the complement-fixation tests were prepared by heavily streaking about fifteen blood agar plates with each strain. The plate cultures were

put in anaerobic jars and incubated for four days at 37 C. The plates were then removed from the desiccators, and the growth was rinsed off with sterile saline solution. It was necessary to use a large wire loop to loosen the growth, as it adhered to the blood agar medium. This growth, when removed, was taken up in about 5 to 6 cc. of saline solution. The suspensions were placed in 15 cc. pyrex centrifuge tubes and alternately frozen and thawed. Freezing was accomplished by putting small blocks of carbon dioxide snow into alcohol and dipping the tubes containing the suspensions into this mixture. After thorough freezing the tubes were held under a hot water faucet, and water at a temperature of 45-50 C. was run over them until the frozen contents were melted. Each antigen was frozen and thawed twenty times. After the final freezing the tubes were centrifugated at high speed for one hour. The supernatant fluid was diluted to 15 cc. with sterile saline solution, placed in sterile vaccine bottles and kept frozen in an electric refrigerator until used. Smears were made of the sediment, but it was difficult, in view of the staining reactions of these organisms, to tell how much autolysis was accomplished by freezing and thawing. The sediment was therefore discarded.

The antigens were not hemolytic or anticomplementary in a 1:4 dilution, so that this dilution was used in the tests. The Kolmer method was followed, using icebox fixation. Antigen 40 did not prove to be antigenic with any of the serums with which it was tested, and for that reason the results from the use of it are not included in the tables (tables 1 and 2).

The complement-fixation test indicated the presence of antibodies in the serum of patients with ulcerative colitis. The antibody titers were not high in any case, but they were greater in the more severe cases (patients 2 and 3 and Mr. L.). No complement-fixing antibodies were found in the serum of patient 1. Following the ileostomy this patient had greatly improved clinically, which might account for the negative tests with her serum.

The results of the complement-fixation tests on monkeys were variable. Following removal of rectal mucosa the antibody titer of the serum of monkey 1 increased, whereas the titer of the serum of monkey 2 was somewhat lower after an operation in which some rectal mucosa was removed. The initial high titer of antibody in the case of monkey 2 may represent a previous ulceration of the bowel in which the antigen in question was present. Epidemics of bacillary dysentery are common in monkeys in captivity, and unless one knows the history of a given monkey one cannot be sure that there was not a previous ulceration of the bowel.

TABLE 1.—*Complement-Fixation Tests on Serum of Patients with Ulcerative Colitis*

Source of Serum with Date Serum Was Taken	Antigen	Result of Test with Serum* 0.1 Cc.	0.05 Cc.
Patient 1 (Mrs. N.), 12/16/33 and 6/2/34	11	—†	—
	38	—	—
	39	—	—
Patient 2 (Mrs. P.), 1/19/34	11	++	—
	38	+++	—
	39	—	—
Patient 3 (Mrs. S.), 5/12/34	11	+++	—
	38	++++	±
	39	+	—
Patient with ulcerative colitis (Mr. L.), 5/12/34	11	+++	—
	38	++++	—
	39	±	—
Patient with ulcerative colitis (Mr. T.), 5/12/34	11	+	—
	38	++	—
	39	±	—
Young woman without history of bowel lesion (Mrs. G.)	11	+	—
	38	+	—
	39	—	—
Four healthy young adults	11	—	—
	38	—	—
	39	—	—

* There was no fixation of complement with 0.025 cc. of serum. Serum controls were not anticomplementary in 0.1 cc.

† A minus sign indicates complete hemolysis; four pluses, no hemolysis.

TABLE 2.—*Complement-Fixation Tests on Serum of Monkeys*

Monkey	Date of Collecting Serum	Treatment of Animal	Antigen	Result of Test with Serum 0.1 Cc.	0.05 Cc.	0.025 Cc.
1	5/ 1/34	Serum taken 9 days after removal of rectal mucosa. Rectal mucosa removed 4/23/34	11	++	±	—
			38	++	±	—
			39	++	±	—
1	5/21/34	More rectal mucosa removed 5/1/34 and 5/9/34. Growth from 6 anaerobic blood agar plate cultures, strain 38, injected submucosally into area of rectum not previously denuded	11	++++	++++	++++
			38	++++	++++	++++
			39	++++	++++	++
1	8/ 4/34	No further treatment	11	++++	++++	+
			38	++++	++++	++
			39	++++	++	—
CP	5/28/34	Had severe diarrhea beginning 10 to 11 days before sample of blood was taken	11	++++	+++	+
			38	++++	++++	+
			39	++++	+	—
CP*	8/ 3/34	Animal was well and healthy	11	++++	++	+
			38	++++	+++	+
			39	++++	++	+
2*	7/17/34	Laparotomy was done 7/17/34 and mucosa removed from rectum	11	++++	+++	+
			38	++++	++++	—
			39	++++	+	—
2	8/ 1/34	Animal was well; bowel had healed	11	+	—	—
			38	++++	++++	—
			39	+	—	—

* Serum slightly anticomplementary; ++ with 0.1 cc. serum; — with 0.05 cc. serum.

AGGLUTINATION TESTS [4]

The first attempts to use cultures grown on anaerobic blood agar plates as antigens in agglutination tests were unsuccessful, as growth removed from these plates tended to stick together in large clumps. Successful antigens were prepared for strain 40 by growing the organism in cystine dextrose beef infusion broth [3] put up in 50 cc. quantities in

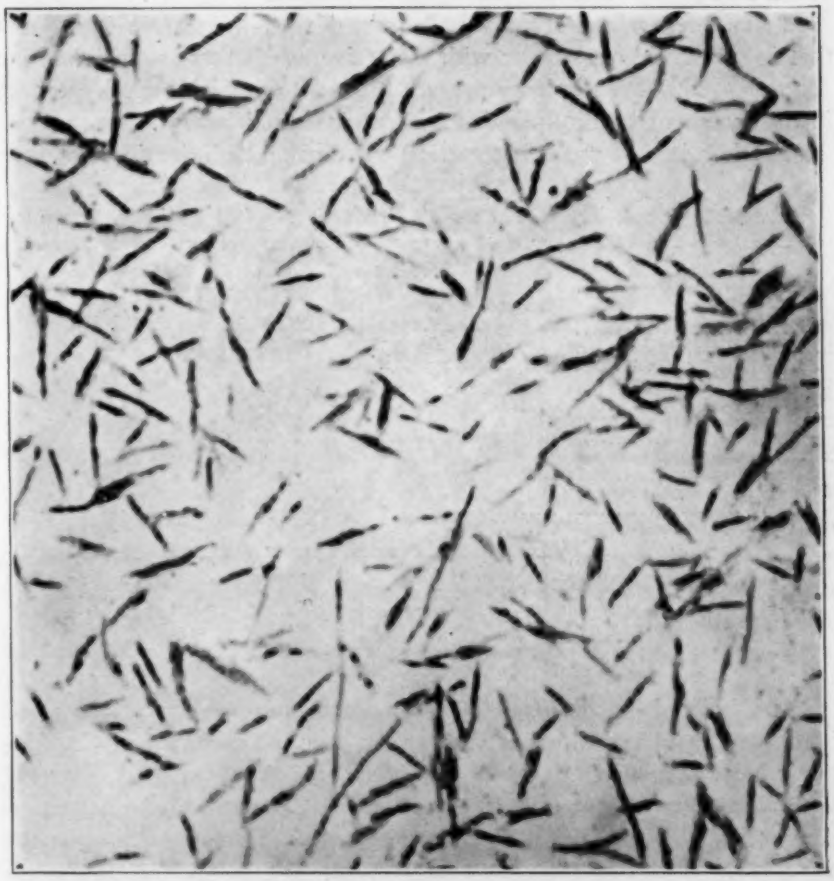

Fig. 8.—Strain 40; anaerobic cystine dextrose broth culture incubated four days at 37 C. Giemsa stain; × 2,100.

flasks and incubated under anaerobic conditions in a desiccator, as previously described. After four days' incubation the growth was centrif-

4. During the progress of the work, two of the strains, 11 and 38, failed to grow following an accident which happened to the desiccator in which the cultures were being incubated. The lid of the desiccator was cracked, thus admitting air and destroying the anaerobic conditions. Strains 39 and 40, however, grew on subculture and were used in later studies.

ugated and the sediment resuspended in sterile 0.85 per cent solution of sodium chloride. The organisms grown in this broth were fusiform, with very pointed ends, and the cells were irregular in staining (fig. 8).

They were gram-negative, and some seemed to contain granules. They were single and uniform in size. Incubation was carried out in a water bath at 45 C. for one hour, after which the flasks were placed in the refrigerator and the readings taken the following day.

From the preliminary results obtained with this strain it appears that in the serum of patients with ulcerative colitis there are agglutinins for this strain, and that they are not present to any considerable extent in the serum of healthy persons without intestinal lesions.

Further studies are being carried out on the agglutination test.

TABLE 3.—*Agglutination Tests with Strain 40 Against Patient's Serum*

Patient	Serum Collected	Result of Test with Given Serum Dilution*					
		1:20	1:40	1:80	1:160	1:320	1:640
1	12/16/33	++	+	—	—	—	—
1	6/ 2/34	+++	++	+	—	—	—
1	11/13/34	++++	++++	+++	+	—	—
2	1/19/34	++++	++++	+++	—	—	—
3	5/12/34	++++	++++	++++	+++	++	+
Miss G., with severe ulcerative colitis	11/21/34	++++	++++	+++	+	—	—
Mr. K., with moderately severe ulcerative colitis	8/22/34	+++	+	+	—	—	—
Three healthy persons† (control)	.....	—	—	—	—	—	—
One healthy person (control)	.....	++	—	—	—	—	—

* Four pluses indicate complete agglutination; a minus sign, no agglutination. No agglutination occurred in a control tube with antigen and saline solution.
† One of these subjects was Mrs. G., referred to in table 1.

COMMENT AND SUMMARY

The isolated colons of the three patients in whom ileostomies had been performed contained at first many species of organisms in relatively large numbers. In the course of months the flora became largely anaerobic. In all three cases the same type of organism eventually predominated. We have not found a description of this organism in the literature. It closely resembled Bacteroides fragilis and funduliformis (Thompson and Beaver [5]), Actinomyces necrophorus (Shaw,[3] Cunningham [6]) and Bacillus necrophorus (Orcutt [7]). There was no zone of clear hemolysis about the colonies on blood agar plates, as described for the aforenamed organisms. A green zone developed about colonies on

5. Thompson, Luther, and Beaver, Donald C.: M. Clin. North America **15**: 1611, 1932.

6. Cunningham, John Sumter: Human Infection with Actinomyces Necrophorus: Bacteriologic and Pathologic Report of Two Cases Terminating Fatally, Arch. Path. **9**:843 (April) 1930.

7. Orcutt, Marion L.: J. Bact. **20**:343, 1930.

anaerobic blood agar plates only after exposure to oxygen. This organism was pathogenic to rabbits and, following subcutaneous injections of large amounts of culture, produced local abscesses which tended to heal after a long time. Necrophorus organisms have a tendency to produce spreading lesions, and rabbits subcutaneously inoculated with them often die from six to seven days after the inoculation. Morphologically and culturally the organisms which we have isolated were similar to the necrophorus organisms. In mediums they produced a putrid odor resembling that of butyric acid. They grew well on blood agar and serum dextrose mediums and in dextrose mediums to which a small amount of cystine was added. Exposure to oxygen was highly lethal in a short period.

An organism similar to this predominating anaerobe was isolated from lesions in the large bowels of monkeys. Probably this organism was present in the normal intestinal tract, since it developed in necrotic membranes formed over areas of rectum which were denuded of mucosa. Attempts to isolate it were often unsuccessful in the presence of large numbers of fecal bacteria. It was not found in the healthy isolated colon in two monkeys (CP and TC [8]) or in monkeys with normal colons. Two monkeys fed a culture of this type of organism (strain 11) did not show any symptoms, and in only one case was the organism demonstrated two days after feeding.

Complement-fixing antibodies have been demonstrated in the serum of four patients with ulcerative colitis, using antigen prepared from the predominating anaerobic organism cultured from the isolated colons of two patients. Very slight fixation of complement occurred with an antigen of monkey origin. The serum of one young adult without a history of bowel lesions gave very slightly positive results, whereas the serum of four other healthy young adults gave negative results. The serum taken from one patient (1) gave a negative reaction. This result is difficult to explain in view of the agglutination reactions, which were positive. There was extensive disease of the bowel in the four cases in which the serum gave positive reactions.

The complement-fixation tests with the serum of the three monkeys tested were all positive but in varying degrees. All of these monkeys were subject to previous pathologic disturbance of the large bowel, for an epidemic of the Flexner type of dysentery occurred spontaneously in the colony at about the time this investigation began. The positive result with the serum from monkey 2, taken on July 17, 1934, might be accounted for on such a basis (table 2).

8. Dack, G. M., and Petran, Elizabeth: Bacterial Activity in Different Levels of Intestine and in Isolated Segments of Small and Large Bowel in Monkeys and in Dogs, J. Infect. Dis. **54**:205 (March-April) 1934.

Agglutination tests were performed using the serum of five patients with ulcerative colitis against strain 40. Agglutinins were present in all of this serum. The serum from three healthy persons contained no agglutinins for this strain, whereas the serum from a fourth healthy person contained only a trace of agglutinins and then only in the strongest dilution of serum. The agglutination test is being studied more intensively.

Further study is necessary before any definite organism may be considered as the causative agent of ulcerative colitis. Bacteriologic and serologic studies in a larger series of cases of ulcerative colitis may help to evaluate the significance of the organism described in this paper.

PEPTIC ULCER FOLLOWING EXPERIMENTAL JEJUNOCOLOSTOMY

PAUL E. McMASTER, M.D.
LOS ANGELES

An unexpected and high incidence of "spontaneous" gastric and duodenal ulceration following jejunocolostomy, which was done for studies other than of peptic ulcer, led to an investigation of this unusual and interesting phenomenon, a preliminary report of which has been made.[1]

Numerous methods have been devised whereby acute, subacute and chronic ulceration of the stomach and duodenum can be produced experimentally. Many important observations on the etiology and pathogenesis of peptic ulcer have been made as a result of experimentation on animals. However, I agree with Ivy and Fauley,[2] who stated that there is still much to be learned about this complex problem. The literature on this subject is far too voluminous to summarize in this article. Among some of the more important articles, in which complete bibliographies dealing with this question may be found, are those written by Mann and Williamson,[3] McCann,[4] Ivy and Fauley,[2] Lindau and Wulff,[5] Matthews and Dragstedt,[6] Cushing,[7] Bollman and Mann,[8] Elman and Hartmann,[9] Konjetzny [10] and Steinberg and Proffitt.[11]

From the Department of Surgery of the University of Chicago.

1. McMaster, P. E.: Experimental Spontaneous Peptic Ulcer, Proc. Soc. Exper. Biol. & Med. **30**:126, 1932.

2. Ivy, A. C., and Fauley, G. B.: The Chronicity of Ulcers in the Stomach and Upper Intestine, Am. J. Surg. **11**:531, 1931.

3. Mann, F. C., and Williamson, C. S.: The Experimental Production of Peptic Ulcer, Ann. Surg. **77**:409, 1923.

4. McCann, J. C.: Experimental Peptic Ulcer, Arch. Surg. **19**:600 (Oct.) 1929.

5. Lindau, Arvid, and Wulff, H.: The Peptic Genesis of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **53**:621, 1931.

6. Matthews, W. B., and Dragstedt, L. R.: The Etiology of Gastric and Duodenal Ulcer, Surg., Gynec. & Obst. **55**:265, 1932.

7. Cushing, H.: Peptic Ulcers and the Interbrain, Surg., Gynec. & Obst. **55**: 1, 1932.

8. Bollman, J. L., and Mann, F. C.: Peptic Ulcer in Experimental Obstructive Jaundice, Arch. Surg. **24**:126 (Jan.) 1932.

9. Elman, R., and Hartmann, A. F.: Spontaneous Peptic Ulcers of Duodenum After Continued Loss of Total Pancreatic Juice, Arch. Surg. **23**:1030 (Dec.) 1931.

10. Konjetzny, G. E.: Chronische Gastritis und Duodenitis als Ursache des Magenduodenol Geschwürs, Beitr., z. path. Anat. u. z. allg. Path. **71**:595, 1923.

11. Steinberg, M. E., and Proffitt, J. C.: The Etiology of Postoperative Peptic Ulcers, Arch. Surg. **25**:819 (Nov.) 1932.

Following the death of two dogs from a perforated duodenal ulcer which developed after the jejunum was sectioned approximately 25 cm. distal to the duodenojejunal junction, both ends being inverted and the proximal stump anastomosed to the colon, it was decided that this occurrence was probably more than merely coincidental. Consequently, studies were designed to determine how often peptic ulceration occurred after jejunocolostomy both with and without retention of the intestine between the points of anastomosis and, if possible, what the etiologic factor might be. In a small series of dogs duodenocolostomy was performed without resecting the intestine between the points of duodenal transection and anastomosis into the colon.

Experimental procedures and observations similar to these were not found recorded in the literature.

METHOD

All operations were performed on healthy adult dogs under anesthesia induced by morphine and ether, with an aseptic technic. Through a right paramedian incision the jejunum was isolated and transected approximately from 20 to 30 cm. distal to the duodenojejunal junction. Both ends of the cut jejunum were inverted with a purse-string suture. A side-to-side anastomosis was then made between the proximal jejunal stump and the ascending colon (fig. 1 *A*). Twenty dogs were used in this series.

In a second series of eleven dogs the jejunum was exposed and sectioned as in the preceding group. The end of the proximal jejunal stump was closed by a purse-string suture, and the rest of the jejunum, all of the ileum and the appendix and the cecum were then excised. The cut end of the stump of the colon was invaginated, and a side-to-side anastomosis was made between the remaining upper part of the jejunum and the colon (fig. 1 *B*).

At no time during the operative procedure was the stomach, the duodenum or the upper part of the abdomen handled or explored in the two series of experiments, thus eliminating the element of trauma to these parts.

Duodenocolostomy was performed on a third series of three dogs. In these experiments the duodenum was sectioned approximately 10 cm. distal to the pylorus; both ends were inverted and an anastomosis was made between the proximal duodenal stump and the colon (fig. 1 *C*). The part of the intestine distal to the point of the duodenal section was left *in situ*.

For the first three postoperative days all the animals were given only physiologic solution of sodium chloride intravenously. Fluids and solid foods were then given by mouth in gradually increased amounts until the stock diet was being fed.

In addition to observations on the occurrence of peptic ulcer following jejunocolostomy, some studies of the blood chemistry were made. These included determinations of cholesterol, sugar, calcium, nonprotein nitrogen and chlorides which were made just before operation and at irregular intervals during the experiments. The weight was recorded throughout the experiments.

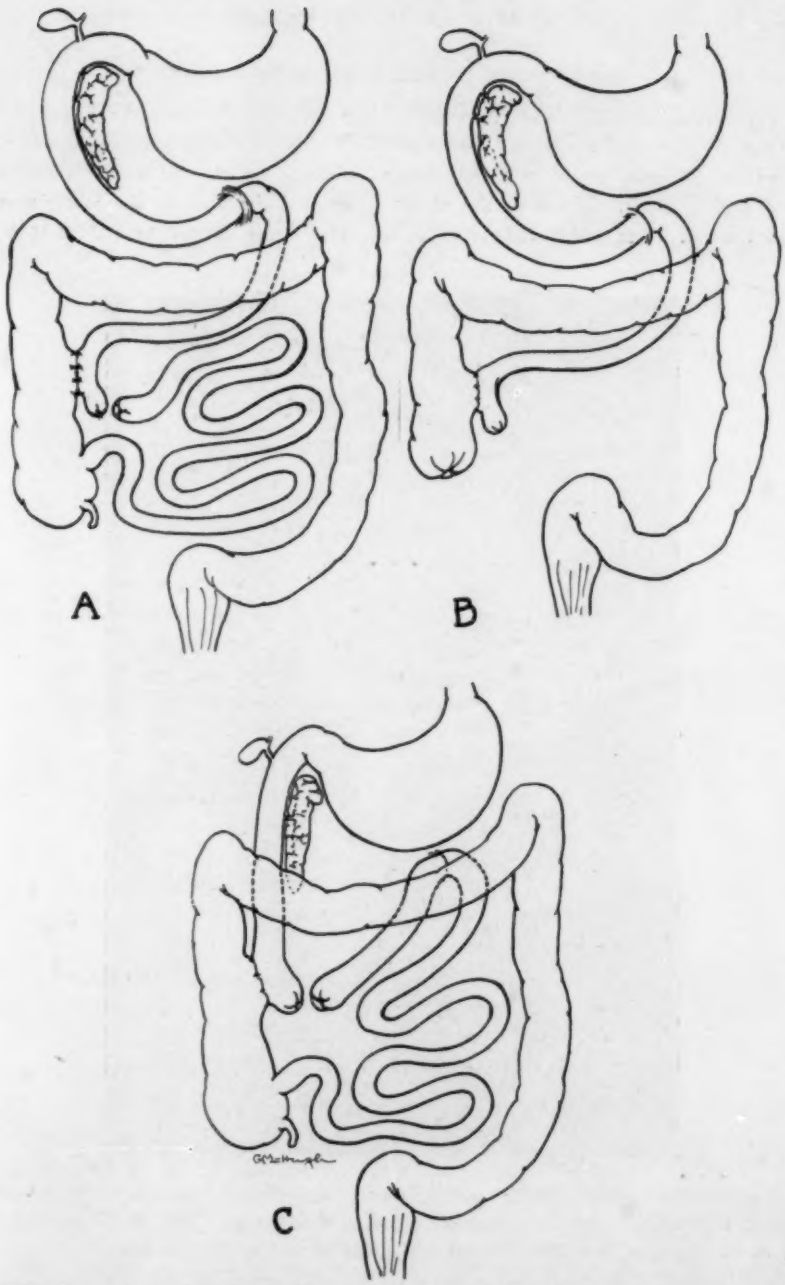

Fig. 1.—*A* is a diagrammatic representation showing jejunocolostomy in which the average distance between the pylorus and the point of jejunal section was 49 cm., and the average length of intestine between the point of section and the ileocecal valve was 278 cm. *B* shows jejunocolostomy in which the average distance from the pylorus to the point of jejunal section was 54 cm. and the average length of intestine resected was 254 cm. *C* shows duodenocolostomy in which the average distance from the pylorus to the point of duodenal section was 10 cm. and the average length of intestine from the point of section to the ileocecal valve was 291 cm.

RESULTS

Jejunocolostomy Without Resection of the Intestine Between the Point of the Jejunal Section and the Anastomosis of the Colon.—Of the twenty dogs in this series, in thirteen, or 65 per cent acute, subacute or chronic peptic ulceration developed (fig. 2). Three of the ulcers perforated the wall of the intestine and caused death from peritonitis (figs. 3 and 4). Most of the animals lost con-

Fig. 2.—Photograph showing multiple acute erosions and ulceration of the prepyloric mucosa, present five days after jejunocolostomy. The distal portion of the small intestine was not excised and remained as a blind stump.

siderable weight, and two at death weighed less than half of their preoperative weight. Both of these had peptic ulcers. Two others that lost practically half of their preoperative weight showed no ulcer of the stomach or duodenum. The average length of life of the dogs in this series was twenty-three days; however, some were killed while in fairly good condition. The shortest time a dog lived

was five days. The longest was one hundred and forty-four days, and at the end of that time the dog was killed. Despite the fact that he had lost considerable weight, his general condition seemed good, and the finding of a large chronic duodenal ulcer which was healing was somewhat unexpected. The average distance from the pylorus to the point of jejunal section in this series was 49 cm. (fig. 5), and the average amount of "short circuited" intestine, or the distance from the point of jejunal section to the ileocecal valve, was 278 cm. The results obtained in this series are shown in table 1.

Fig. 3.—Photograph showing a large perforated duodenal ulcer and a subacute prepyloric ulcer, present forty-three days after jejunocolostomy. The distal portion of the small intestine was not excised. The dotted line indicates the pylorus.

Jejunocolostomy with Resection of the Distal Portion of the Jejunum and All of the Ileum, Appendix and Cecum.—Eleven dogs were used in this series, and peptic ulceration developed in only two, giving an incidence of 18 per cent. One of the dogs showed acute erosions of the gastric mucosa, and another showed both acute and subacute lesions. The dog in this series which survived the longest lived for ninety-four days and lost nearly 60 per cent of his preoperative weight, but peptic ulceration did not occur. The shortest length of time a dog

in this series lived was ten days, and the average for the eleven dogs was thirty-four days. Each of the animals in whom peptic lesions developed weighed at death only half of the preoperative weight. Four others that lost practically as much weight showed no peptic ulceration.

The dogs ate well but showed a gradually increasing loss of weight. Only when the condition which caused death set in did anorexia develop. Diarrhea was noted occasionally but for the most part was not a conspicuous symptom.

Fig. 4.—Photograph showing a large perforated duodenal ulcer, present thirty-seven days after jejunocolostomy. The distal portion of the small intestine was not excised. The dotted line indicates the pylorus.

The longest segment of intestine resected in any animal measured 326 cm. and the shortest 132 cm. The average length was 254 cm., and the average distance from the pylorus to the point of jejunal severance was 54 cm., corresponding with that portion of the small intestine through which food passed before entering the colon. In two of the experiments studies of the blood chemistry were made, and

no essential changes were found in the amount of cholesterol, sugar, calcium, chlorides or nonprotein nitrogen. The results obtained in this series are shown in table 2.

Duodenocolostomy Without Resection of the Intestine Distal to the Point of Duodenal Section.—In three dogs subjected to this operation peptic ulceration did not occur. The average length of intestine between the point of duodenal section,

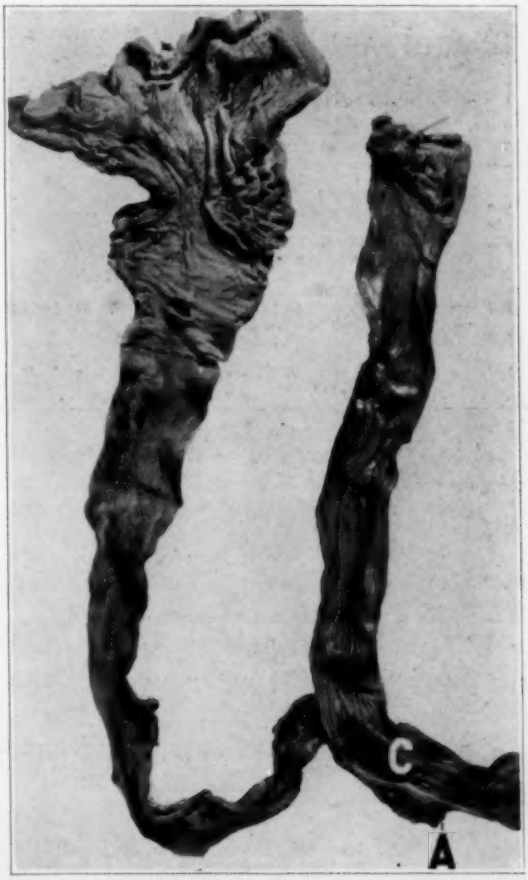

Fig. 5.—Photograph showing a large subacute prepyloric ulcer. The point of jejunal section (*A*) was 38 cm. distal to the pylorus (dotted line). The anastomosis of the jejunum to the proximal ascending colon is shown at *C*. The distal portion of the small intestine was not excised.

which was approximately 10 cm. distal to the pylorus, and the ileocecal valve was 291 cm. Twenty-three days was the average postoperative length of life of these dogs. In one the loss of weight was 50 per cent, while in the other two it was less. The results obtained in this series are shown in table 3.

TABLE 1.—*Jejunocolostomy Without Resection of Intestine*

Dog	Jejunal Section Distal to Pylorus, Cm.	Jejunal Section Proximal to Ileocecal Valve, Cm.	Length of Experiment, Days	Autopsy Observations	Preoperative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
275	53	216	7	Intussusception	14	11.6	0
243	60	210	144	Large, chronic duodenal ulcer, pneumonia	12	7.5	+
283	71	360	43	Peritonitis; perforated duodenal ulcer and one subacute gastric ulcer	16.8	6.8	+
223	45	300	40	No peptic ulcer; three large acute ulcers of the colon	13.6	7	0
226	36	245	30	Gastric ulcer; walled off, perforated duodenal ulcer	11.6	5.2	+
473	61	500	7	Duodenal mucosal hemorrhages; no ulcers; had diarrhea with huge quantities of blood	23	18	0
474	58	395	5	Peritonitis; anastomotic leak	21.2	19	0
476	38	222	26	Two gastric ulcers; one acute and one subacute	9.4	5.1	+
471	43	302	14	Acute gastric ulceration	9.9	5.1	+
527	100	380	8	Acute prepyloric ulcers; pneumonia	33.2	25.8	+
530	30	212	8	Pneumonia	9.7	6.1	0
525	38	255	16	No peptic ulcers; pneumonia	9	4.5	0
562	38	235	18	Multiple gastric erosions; one duodenal and one prepyloric ulcer	9	5.4	+
576	39	246	12	No ulcers; cachexia	6.4	3.9	0
575	41	252	9	Pneumonia; acute gastric erosions	8.8	6	+
572	41	230	16	Infection in skin wound; many acute gastric erosions	8.8	5	+
597	40	260	37	Perforated duodenal ulcer; peritonitis	7.9	4.2	+
659	43	260	35	Pneumonia; subacute and acute peptic ulceration	8.3	4.2	+
649	38	230	5	Pneumonia; acute ulcers of the stomach	9	5	+
220	60	250	50	Killed; multiple acute gastric ulcers	17.4	9	+

TABLE 2.—*Jejunocolostomy with Resection of the Distal Portion of the Jejunum, and the Ileum, Appendix and Cecum*

Dog	Jejunal Section Distal to Pylorus, Cm.	Intestine Resected, Cm.	Length of Experiment, Days	Autopsy Observations	Preoperative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
701	48	295	94	Cachexia; no ulcers; no pneumonia	18.4	8.8	0
702	63	275	11	Pneumonia	11.2	6.2	0
660	69	325	56	Perforated jejunal anastomotic ulcer associated with silkworm gut suture; multiple acute gastric erosions	25	13.8	+
696	36	132	10	Pneumonia; no ulcers	9.6	6	0
715	45	280	10	Distemper; no ulcers	12.4	9	0
692	50	175	11	Peritonitis; anastomotic leak; no ulcers	8	6	0
732	60	315	14	Distemper; no ulcers	21	14.2	0
767	54	292	45	Perforated jejunal ulcer associated with silkworm gut suture; no peptic ulcers	17.4	10.8	0
644	55	190	57	Cachexia; no ulcers	6	3	0
838	68	326	45	Early stages of pneumonia; three acute gastric ulcers	24.2	12.2	+
848	64	285	17	Pneumonia; no ulcers	21.8	14.2	0

TABLE 3.—*Duodenocolostomy Without Resection of Intestine*

Dog	Duodenal Section Distal to Pylorus, Cm.	Duodenal Section Proximal to Ileocecal Valve, Cm.	Length of Experiment, Days	Autopsy Observations	Preoperative Weight, Kg.	Weight at Death, Kg.	Peptic Ulceration
281	9	328	22	Pneumonia; no irritation of the colon; no ulcers	13.5	8	0
227	9	240	28	Emaciated; no irritation of the colon; no ulcers; cause of death (?)	7	3.5	0
274	10	305	18	Pneumonia; no ulcers	10	6.5	0

COMMENT

In a study of microscopic sections from the various peptic lesions which were found in the foregoing experiments all stages of ulceration were noted. These ranged from early stages of acute erosions, of which some extended to the muscularis mucosae and others involved only the superficial mucosae, with a slight surrounding inflammatory reaction, to typical chronic ulcers with punched-out borders and deep bases. A few had perforated the intestinal wall. Practically all of the lesions were associated with chronic inflammation and lymphocytic infiltration of the surrounding muscularis. This condition was slight in the acute lesions but became progressively more intense as the severity and chronicity of the ulceration increased. This observation does not seem to substantiate the work of Konjetzny,[10] who expressed the belief that chronic gastritis and duodenitis were the predisposing cause of peptic ulceration. The amount of inflammatory reaction in the stomach and duodenum associated with the peptic ulceration in the preceding experiments seemed to follow, and be in direct proportion to, the age and chronicity of the ulcerations rather than to precede the onset of the acute lesions.

It is of interest to note that in some of the animals multiple lesions were found which exhibited different stages of ulceration, ranging from acute erosions to more chronic ulcers (fig. 6). This suggests that acute erosions or ulcerations may lead to chronic peptic ulcers, although Spira [12] stated that this does not occur.

No definite etiologic factor seems apparent to explain why the peptic ulcers formed "spontaneously." If the upper part of the abdomen had been explored, the stomach or duodenum traumatized or handled or some disturbance produced in the bile or pancreatic ducts in such a way that the secretions were diminished or eliminated, a more definite explanation might be propounded. But in the absence of any of these factors other causes must be considered.

It has been suggested by some authors that loss of weight and decreased resistance with resultant cachexia might lead to peptic ulceration. This hardly seems tenable in the light of the present experiments, for if this were true why did the dogs with extensive intestinal resections, in each of whom there was a marked loss of weight, show an incidence of ulceration of only 18 per cent while the dogs on whom the same operation was performed except that the intestine was left in situ showed an incidence of 65 per cent? Also, in the three experiments of duodenocolostomy in which the dogs lost considerable weight, ulcera-

12. Spira, J. J.: The Causation of Chronic Gastro-Duodenal Ulcers, New York, Oxford University Press, 1931.

tion in the stomach or duodenum did not occur. Hence it does not seem that severe loss in weight or cachexia is the sole explanation.

At autopsy, in the animals in which the small intestine was not excised, there was found in the lumen of the ileum an "inspissated, thick, yellow, cheesy material." Some of this substance was like food which might have been regurgitated through the ileocecal valve and

Fig. 6.—Photograph showing mucosal hemorrhages in the fundus of the stomach. Multiple erosions, acute ulcerations and also a rather large subacute ulcer in the prepyloric region were present eighteen days after jejunocolostomy. The distal portion of the small intestine was not excised.

carried up the intestinal tract by reverse peristalsis. The other portion of this material was apparently excretory and secretory products from the intestinal canal. The impression obtained from observing this substance was that normal intestinal peristalsis, especially in the lower part of the ileum, had been greatly altered and a condition of intestinal stasis

had resulted. As it was thought that this factor might possibly decrease the normal gastric emptying time, thus exposing the mucosa of the stomach to the acid gastric contents for a longer time and predisposing it to peptic ulceration, comparative fluoroscopic studies of several animals, with and without resections of the intestine, were made preoperatively and at irregular postoperative intervals. The results were somewhat inaccurate owing to technical difficulties, but in a few observations which appeared fairly accurate there were no pronounced changes in the emptying time of the stomach.

Owing to the decrease in the absorptive space of the bowel in these experiments, essential organic or inorganic substances probably passed through the shortened intestinal tract without being assimilated. Dalldorf and Kellog [13] noted gastric ulcers developing in albino rats fed diets deficient in vitamin B. The possibility of deficiency in some vitamin influencing the occurrence of peptic ulceration in the aforementioned experiments is only an interesting speculation. No definite observations giving results either for or against this possibility were made.

As the greatest incidence of gastroduodenal ulceration occurred in the animals in which the intestine had not been resected, this portion of the intestine seems to be the most logical place to look for the etiologic factor. With a condition of "stasis" present in the remaining "inactive" small intestine the likelihood of bacteria or toxins being absorbed and influencing peptic ulceration must be considered. Rosenow [14] in his work on the causation of peptic ulcer considered foci of infection important. He mentioned that among the many foci the intestinal tract, which for mechanical reasons can neither drain nor heal well, should be regarded as a test tube with permeable walls embedded in the tissues. He has been able to demonstrate in stained sections of the intestine the presence of streptococci in the tissues surrounding the peptic ulcer. Also by cultures of fresh specimens from ulcers, he has isolated these bacteria, which when injected into experimental animals have caused peptic ulceration. Neither cultures of the ulcers in the foregoing experiments nor stains of microscopic sections for the presence of these bacteria were made.

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13. Dalldorf, G., and Kellog, M.: Incidence of Gastric Ulcer in Albino Rats Fed Diets Deficient in Vitamin B (B_1), J. Exper. Med. **56**:391, 1932

14. Rosenow, E. C.: The Production of Ulcer of the Stomach by Injection of Streptococci, J. A. M. A. **61**:1947 (Nov. 29) 1913. The Causation of Gastric and Duodenal Ulcer by Streptococci, J. Infect. Dis. **19**:333, 1916. Focal Infections and Elective Localization of Bacteria in Appendicitis, Ulcer of the Stomach, Cholecystitis and Pancreatitis, Surg., Gynec. & Obst. **33**:19, 1921. Focal Infection and Elective Localization, Internat. Clin. **2**:29 (June) 1930.

SUMMARY

Following jejunocolostomy in which the distal portion of the jejunum and the ileum were left in situ as a blind stump, acute, subacute or chronic peptic ulceration was noted in thirteen, or 65 per cent, of twenty dogs operated on. Three of the ulcers perforated the wall of the intestine, leading to peritonitis. In three dogs on which duodenocolostomy was performed, leaving the distal portion of the duodenum, the jejunum and the ileum as a blind stump, peptic ulceration was not noted.

When a jejunocolostomy was performed with resection of the intervening bowel, peptic ulceration occurred in two, or 18 per cent. of eleven dogs operated on.

A rather marked loss of weight occurred in nearly all of these animals, but this did not seem to be the etiologic factor responsible for the peptic ulcers.

Gastritis and duodenitis, as evidenced by inflammatory reaction in the surrounding walls of the stomach and duodenum, seemed to follow rather than precede the peptic ulceration, as nearly as could be determined by microscopic studies.

1930 Wilshire Boulevard.

INFECTIOUS GANGRENE OF THE SKIN DUE TO BACTERIAL SYNERGISM

WITH PARTICULAR REFERENCE TO NOMA AND POSTOPERATIVE CUTANEOUS GANGRENE

N. FREDERICK HICKEN, M.D.
OMAHA

Gangrenous infections of the skin and subcutaneous tissues are much more common than is usually appreciated. These necrotizing processes develop rapidly, destroying the involved tissues and jeopardizing the lives of the patients. Fusospirochetal, amebic and streptococcic infections, ecthyma, gas gangrene and phagedenic ulcers of the thoracic and abdominal walls following operations for suppurative processes are the most common clinical expressions of bacterial gangrene of the skin.

Accurate diagnosis and scientific treatment depend on the identification of the invading organisms as well as on an appreciation of the local tissue reaction and the systemic response to such infections. Meleney [1] maintained that complete bacteriologic studies, employing anaerobic as well as aerobic methods, are necessary if one expects to isolate the provocative organisms. Cultures should be made from biopsy specimens taken from various areas of the lesion. By such painstaking bacteriologic examination, he has demonstrated that a bacterial synergism, or a symbiotic relationship between certain bacteria, is responsible for these gangrenous lesions.

Recently I have seen two patients with such conditions: one had a gangrenous stomatitis (noma) associated with acute myelogenous leukemia, and the other had a large sloughing necrotic ulcer of the thoracic wall following a thoracotomy for empyema. Both lesions were very destructive. They spread rapidly and produced severe systemic reactions similar to those seen with virulent bacterial infections. Bacteriologic and experimental studies indicated that both lesions were due to bacterial synergism and hence were of sufficient interest to merit reporting.

From the Departments of Anatomy and Surgery, University of Nebraska.

1. Meleney, F. L.: Hemolytic Streptococcal Gangrene, Arch. Surg. **9**:317 (Sept.) 1924; A Differential Diagnosis Between Certain Types of Infectious Gangrene of the Skin, with Particular Reference to Hemolytic Streptococcus Gangrene and Bacterial Synergitic Gangrene, Surg., Gynec. & Obst. **58**:847, 1933.

A CASE OF NOMA

History.—A Negro boy, aged 3, was admitted to the University of Nebraska Hospital because of a "sore mouth."

He was well until three weeks prior to admission, at which time his ankles, wrists and right shoulder were painfully swollen. Examination at the dispensary revealed enlargement and congestion of the tonsils, diffuse bilateral cervical adenopathy, and inflammatory periarticular swelling of the hands, feet and ankles. Within two weeks' time the "rheumatic pains" had subsided and the boy felt well. Apparently he had had mild inflammatory arthritis, which was thought to be related to the tonsillar infection; therefore, a tonsillectomy was advised just as soon as his general condition permitted. Unfortunately no hematologic studies were made at the dispensary.

Fig. 1.—The gangrenous noma has perforated the cheek. Note the induration and inflammatory swelling surrounding the ulcerative area.

A week later while chewing gum he bit the inner surface of the right cheek. Within two days, the entire cheek was swollen, tender and painful. He refused to eat. His breath became offensive. Four days after the original trauma, his mother noticed a large sloughing ulcer on the inner surface of the right cheek. Hot packs and irrigations of the mouth merely aggravated the condition, so the child was returned to the dispensary.

Physical Examination.—The patient was a well nourished Negro boy with a temperature of 101.3 F.; his pulse rate was 120 beats per minute; his respirations were 18. The right cheek, the right side of the nose and both lips were swollen, firm and hyperemic. On the inner surface of the cheek was a large sloughing ulcer which was covered with a gray necrotic membrane. This membrane was easily removed, leaving a dark nonbleeding ulcer base. The ulcer not only had spread peripherally but had directly invaded the soft tissues of the cheek. The

gums were swollen and tender but presented no areas of ulceration, necrosis or bleeding. The tonsils were enlarged, and plugs of inspissated material could be expressed from the tonsillar crypts. The breath had a repulsive fetid odor.

The cervical lymph nodes were hypertrophic, firm, fixed and discrete, but not tender. The inguinal, axillary, epitrochlear and popliteal nodes were small, firm and "shotlike." The liver extended 1 fingerbreadth below the costal margin; it was smooth, moved with respirations and was not tender. The spleen could not be palpated.

According to the blood count on admission, there were 5,200,000 erythrocytes, with a hemoglobin percentage of 73. There were 44,500 leukocytes, with a differential count of 43 per cent polymorphonuclear segmented cells, 10 per cent staff forms, 12 per cent young forms, 5 per cent myelocytes, 1 per cent promyelocytes, 2 per cent blast cells, 10 per cent lymphocytes, 15 per cent monocytes and 2 per cent unidentified forms. Forty-four nucleated and other immature red cells were seen while the white cell count was being made. Fifty-nine per cent of the leukocytes gave a positive oxidase reaction. Apparently the child had acute myelogenous leukemia complicated by ulcerative stomatitis.

Treatment and Course.—Active therapy consisted of intramuscular injections of neoarsphenamine, irrigations of the oral cavity with oxidizing solutions such as potassium permanganate and sodium perborate, and applications of moist and dry heat every three hours. Repeated transfusions of whole blood were given in an attempt to stimulate his defensive mechanism.

In spite of these therapeutic attempts, the ulceration spread rapidly; his condition became very toxic; his pulse rate increased to 130 beats per minute, and his temperature varied from 100 to 101.8 F. After two weeks the right side of his face was intensely swollen, and the brawny induration had increased. The skin overlying the central portion of the inflammatory tumor had a peculiar brownish discoloration; it rapidly became black and gangrenous, and finally the ulcer perforated. This large, foul-smelling, perforating ulcer, which permitted the constant drooling of saliva, combined with the extensive inflammatory swelling of the face presented a most gruesome sight.

On the thirty-ninth day of his stay in the hospital the patient was seen in surgical consultation, and I felt that even in the presence of leukemia the necrotizing ulcer should be excised. This would not materially influence the course of the leukemia, but removal of the gangrenous, decomposing tissue with its resultant infection would make nursing care more pleasant and reduce the absorption toxemia.

Under avertin narcosis, all the diseased tissue, which constituted the right cheek and part of the upper and lower lips, was removed by cautery excision. The periosteum and the cortical portion of the maxilla were diseased, and this infected tissue was removed with a curet. Hot fomentations and frequent irrigations soon stimulated the growth of healthy granulation tissue.

The child made an excellent response until the ninth postoperative day. He then contracted an epidemic streptococcic sore throat and laryngitis which finally terminated in bilateral bronchopneumonia. He seemed unable to combat this widespread systemic infection, for his resistance was very low. Seventeen days after the first operation, it was necessary to excise a portion of the necrotic gingival tissue from the maxilla and mandible and to extract four teeth. The infected bone was removed by curettement. The ulceration, however, continued, and for a third time the diseased portions of the cheek and lip were removed. During the remainder of his hospitalization there was no recurrence of the nomatous process.

Fig. 2.—Appearance of the face after excision of the noma. The mucous membrane is rapidly covering the denuded areas.

Fig. 3.—Acute streptococcic dermatitis of the ear, face, neck and trunk. Nonhemolytic streptococci were recovered from the vesicular fluid. There was no evidence of preexisting noma.

On the twenty-second postoperative day a small vesicle appeared on the inner surface of the left external ear. In five hours the entire ear was covered with a large "blister." The epidermis was separated from the dermis by a clear yellow fluid. When the top of the vesicle was removed, the dermis appeared very red and hyperemic and was very painful. No ulceration, necrosis or gangrene was seen. Within two days' time the inflammatory process had practically subsided. Three days later a similar bleb appeared in the suprasternal notch, and after six hours it had completely covered the right side and posterior portions of the neck. The epidermis seemed to float on top of this yellow serous exudate, from cultures of which grew nonhemolytic streptococci. Five days later several small vesicles developed in the interscapular area, became confluent and quickly encircled the entire trunk. Nonhemolytic streptococci were recovered from this vesicular fluid. Careful examination did not reveal any abscesses, necrosis or gangrene of the dermal tissues.

The child died on the thirtieth postoperative day from acute myelogenous leukemia, bronchopneumonia and acute streptococcic dermatitis. There was no evidence of the preexisting noma; in fact, the oral mucosa was rapidly covering the denuded areas.

COMMENT

Noma is a progressive gangrenous ulcer, usually involving the oral cavity. However, it may affect any part of the body. For example, Pollard [2] observed a "nomatous ulcer" of the leg. Henoch [3] described a similar lesion of the vulva and labia. Holt [4] reported seven instances in which the "noma" originated in the external auditory canal or the middle ear, where it had been superimposed on long-standing otitis media. Noma is usually seen as a complication of measles, typhoid fever, scarlet fever, diphtheria, pneumonia or leukemia; in fact, any disease which materially lowers the resistance of the host may be a precursor of this malady. Portmann [5] observed a case of noma which occurred spontaneously without any preceding infection, but this is very unusual.

The destructive nature of noma has caused it to be confused with malignant lesions, for it has been frequently referred to as "cancrum oris," "water cancer," "scorbutic cancer," etc. Since the advent of bacteriology, numerous organisms have been recovered from these gangrenous lesions, each one of which has been thought to be the causative factor. The fusiform bacillus, the spirochete, the streptococcus, the staphylococcus, the streptothrix, the cladothrix and the

2. Pollard, quoted by Weaver, G. H., and Tunnicliff, R.: Wien. klin. Wchnschr. **18**:1236, 1905.

3. Henoch, E.: Vorlesungen über Kinderkrankheiten, Berlin, A. Hirschwald, 1890, p. 464.

4. Holt, L. E.: Diseases of Infancy and Childhood, ed. 10, New York, D. Appleton & Company, 1920.

5. Portmann: Noma Arising Spontaneously, cited in Kauffman, Edward: Pathology for Students and Practitioners, translated by P. Reimann, Philadelphia, P. Blakiston's Son & Company, 1929, vol. 1, p. 552.

diphtheria bacillus have been the most frequent invaders. Vincent [6] maintained that the spirochete and the fusiform bacillus were the provocative agents. Sobel and Hermann [7] believed that the fusiform bacillus and the spirochete were the same organism in different phases of development. Weaver and Tunnicliff [8] and Rona [9] thought the fusiform bacillus to be the etiologic agent and the spirochete merely an incidental invader. Walsh [10] studied eight cases of noma and felt that the diphtheria bacillus was responsible for the necrotic ulceration. Ranke,[11] Holt [4] and Verhoeff [12] maintained that the streptococcus was the most important pathogenic factor. Great difficulty was encountered in determining which organisms were responsible for the actual death and disintegration of the tissues and which were merely incidental invaders. Many bacteria escaped detection because anaerobic cultures were not made. Thus the pathogenicity of noma remains an open question.

With the hope of shedding some light on this problem, Dr. P. M. Bancroft of the department of bacteriology made anaerobic and aerobic cultures on many different mediums from pieces of tissue taken for biopsy from various portions of the nomatous ulcer. From the surface of the ulcer itself, he recovered fusiform bacilli, spirochetes, nonhemolytic streptococci, Staphylococcus aureus, diphtheroid bacilli and many gram-negative bacilli. From a small piece of tissue excised from the zone of reaction, he obtained growth of pure strains of anaerobic microaerophilic nonhemolytic streptococci, anaerobic fusiform bacilli and anaerobic Staph. aureus. Both the streptococci and the staphylococci grew in aerobic conditions also. All anaerobic cultures were grown in a vacuum tank in which the proper tension and concentration of carbon dioxide and hydrogen could be maintained. Mixed cultures of the three latter organisms presented the same offensive fetid odor as did the nomatous lesion of the patient.

Microscopic studies of the gangrenous ulcer confirmed the bacteriologic findings and demonstrated three distinct types of reaction to this infection. In the gangrenous area, all tissues had become necrotic, losing their morphologic characteristics. The cell nuclei were pyknotic

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6. Vincent, H.: Sur l'étiologie et sur les lésions anatomopathologiques de la porriture d'hospital, Ann. Inst. Pasteur **10**:488, 1896.

7. Sobel, J., and Hermann, Charles: Ulceromembraneous Angina Associated with Fusiform Bacilli (Vincent): Report of Twelve Cases in Children, New York M. J. **74**:1037 and 1043, 1901.

8. Weaver, G. H., and Tunnicliff, R.: Noma, J. Infect. Dis. **4**:8, 1907.

9. Rona: Arch. f. Dermat. u. Syph. **67**:259, 1903.

10. Walsh: Proc. Path. Soc., Philadelphia **4**:179, 1901.

11. Ranke, quoted by Weaver, G. H., and Tunnicliff, R.: München med. Wchnschr. **47**:1485, 1900; **49**:1787, 1902; **50**:13, 1903.

12. Verhoeff, F. H.: J. Boston Soc. M. Sc. **5**:461, 1900.

and fragmented, the cell walls had disintegrated, and the entire mass of necrotic tissue stained homogeneously. In the zone of reaction a very different condition prevailed. The walls of the blood vessels were slightly thickened, and their lumens were plugged with obstructing thrombi. As one approached the normal tissue the lumens of the vessels were patent but contained clumps of degenerating erythrocytes. Scattered throughout the zone of reaction were rod-shaped bacilli with rounded ends. They had invaded the skin and subcutaneous tissues and were either clumped together or arranged in a palisade formation. Isolated groups and short chains of cocci were frequently seen, some of which had been engulfed by polymorphonuclear phagocytes. In the marginal zone—the junction of the normal and diseased tissue—there was a mild inflammatory reaction; all tissues were hyperemic, and the blood vessels were engorged; there was some polymorphonculear infiltration but no leukemic change.

As these studies failed to show any evidence of leukemic infiltration it was apparent that the nomatous ulcer was due to an active bacterial infection. The bacterial toxins and products, combined with the thrombosis of the blood vessels, accounted for the necrosis and devitalization of the facial tissues. The presence of a mixed infection suggested the possibility of bacterial synergism, so the following experimental studies were made.

EXPERIMENTAL DATA

If noma is an infective bacterial gangrene, what are the provocative micro-organisms?

As previously stated, anaerobic and aerobic cultures were made from the surface of the gangrenous and necrotic areas, from which nonhemolytic streptococci, Staph. aureus, pneumococci, diphtheroid bacilli and unidentified gram-negative bacilli were isolated. In order to determine the pathogenicity of these organisms, animal inoculations were made. One cubic centimeter amounts of a suspension of the nonhemolytic streptococci in physiologic solution of sodium chloride were injected into the abdominal skin of rabbits and guinea-pigs. Similar procedures were carried out with each of the other organisms. The nonhemolytic streptococci caused a mild local dermatitis which completely subsided within forty-eight hours. Staph. aureus produced a small subcutaneous abscess with a mild inflammatory dermatitis, both reactions disappearing after four days. The guinea-pigs seemed much more sensitive to these injections than the rabbits. Suspensions of pneumococci, diphtheroid bacilli and gram-negative bacilli each failed to initiate any dermal reaction. These organisms were then used in various combinations, and only a very mild localized dermatitis resulted, with no evidence

of ulceration, necrosis or gangrene at the sites of injection. Furthermore, when a mixed suspension of all these bacteria was injected into the abdominal skin of these laboratory animals, only a mild cutaneous reaction occurred. Thus we were unable to reproduce a "nomatous-gangrene" by the intracutaneous injection of either a pure or a mixed bacterial suspension of the organisms found on the surface of the necrotic facial ulcer.

Since we had failed to isolate the causative bacteria from the surface of the gangrenous process, it became evident that the inciting organism might be confined to the tissues at the margin of the advancing inflammatory lesion. Under strict aseptic precautions, small pieces of tissue were removed from the zone of reaction, and both anaerobic and aerobic cultures made. Anaerobic micro-aerophilic nonhemolytic streptococci, fusiform bacilli and anaerobic and aerobic Staph. aureus were found in abundance. No diphtheroid bacilli, gram-negative bacilli or pneumococci were found, indicating that these were merely incidental surface invaders of the gangrenous tissues. In attempting to reproduce the noma, 1 cc. amounts of a suspension of fusiform bacilli in physiologic solution of sodium chloride were injected intracutaneously into the guinea-pigs and rabbits. Repeated attempts failed to elicit even the slightest tissue response. Similar injections of anaerobic nonhemolytic streptococci resulted in an evanescent localized dermatitis. The staphylococci produced small subcutaneous abscesses, but no ulceration appeared. Combinations of any two of these organisms caused only mild inflammatory reactions of the skin. In no instance was there tissue destruction or necrosis.

A mixed bacterial suspension consisting of the fusiform bacilli, the staphylococci and the nonhemolytic streptococci was now introduced into the skin of the test animals. Within twenty-four hours' time there was a pronounced local tumefaction. The skin became inflamed, hyperemic and very tender. At the end of seventy-two hours, the hyperemic tumors measured 3 cm. in diameter, and the overlying skin had acquired a brownish hue. The tumor mass did not fluctuate. Within ninety-six hours a small ulceration measuring 2 mm. in diameter appeared at the site of injection. Its borders were sharply demarcated, giving it a punched-out appearance. During the next twenty-four hours the ulcer spread until it measured 2.5 cm. in diameter. Its margins were black and gangrenous, the skin and subcutaneous tissues were undermined, and the fascia overlying the abdominal muscles was destroyed. No bleeding occurred from small incisions made into the borders of the ulcer. The tissues were edematous and indurated. The necrotizing ulcer rapidly increased in size until it measured 5 cm. in diameter. It then seemed to remain stationary for five days. The general appearance of the animal improved, signs of tissue repair appeared,

and within two weeks' time the lesion had completely healed. The rabbits seemed more resistant to these infections as only very small ulcerations appeared at the sites of injection, and these healed rapidly.

Microscopic studies of the ulcer tissue from the guinea-pig revealed a much more fulminating process than was present in the patient's ulcer. Considerable leukocytic infiltration, areas of abscess formation, marked hyperemia and congestion of all tissues were seen. Groups of cocci had been phagocytosed by the polymorphonuclear cells. In the gangrenous areas the morphologic characteristics of all dermal structures had been destroyed.

From these experimental studies, it is apparent that the nomatous ulcer was due to a bacterial synergism between the fusiform bacilli, the anaerobic nonhemolytic streptococci and Staph. aureus. Individually these organisms were incapable of reproducing the noma, but combined they effected a rapidly progressing phagedenic ulcer which completely destroyed the involved tissues. Of course, one must always view animal experimentation with reservation, but such studies as these are more than suggestive, for they present strong evidence that noma is caused by bacterial symbiosis.

This concept is further corroborated by other clinical observations. Remember that this patient had two dermal lesions, one a true nomatous ulcer and the other a streptococcic dermatitis. This streptococcic infection was extremely virulent, rapidly destroying the epidermis and evoking a pronounced hyperemia of the dermis with resultant serous effusion. Nonhemolytic streptococci were isolated from both lesions. Why, then, did not the areas of dermatitis actively infected with streptococci undergo gangrenous changes? The patient's general condition favored a nomatous development, for such a lesion had already been produced. Why did not noma develop in these large denuded areas of dermatitis? Simply because the streptococcus alone could not produce a noma. Remember, then, that when injected intradermally into animals, the streptococci did not produce necrosis of tissue but merely a localized dermatitis. It evidently required the symbiotic relationship between the anaerobic nonhemolytic streptococci, the fusiform bacilli and the staphylococci to produce the gangrenous changes in the dermal structures which resulted in noma.

Why did the experimental noma heal? Is not noma in most instances fatal? Gangrenous stomatitis or noma is not a fatal disease of itself, and the literature contains many reports of spontaneous recovery. It is true that many patients with noma die, but they die from the primary diseases—the leukemia, bronchopneumonia, scarlet fever, typhoid fever, etc.—and not from the noma. It must be remembered that the guinea-pigs were very healthy animals, but in spite of this the phagedenic gangrenous ulcers grew rapidly until sufficient time had elapsed to

permit the development of an active defense mechanism in these animals; then the necrotizing process was arrested and the ulcer healed. If some systemic disease had prevented the guinea-pig from marshaling an adequate resistance against the bacterial gangrene, it is easy to see how the lesions would finally have become very extensive.

The experimental and clinical evidence which has been presented in this case indicates that the noma was an infective gangrene due to bacterial synergism, and that it was not related to the leukemic process.

A CASE OF POSTOPERATIVE INFECTIVE GANGRENE OF THE SKIN

Chronic infective gangrene of the skin is occasionally seen following operation for drainage of deep-seated abscesses of the peritoneal and thoracic cavities. Meleney,[1] and later Brewer and Meleney,[13] carefully analyzed such infections and concluded that they were due to bacterial symbiosis, usually that of streptococci and staphylococci. Cullen,[14] Alexander,[15] Gillespie,[16] Shipley,[17] Ballin and Morse,[18] Lynn,[19] Meleney,[1] Baker and Terry,[20] Horsley [21] and others have reported large sloughing gangrenous ulcers of the abdominal wall following the drainage of intraperitoneal abscesses. Christopher,[22] Ballin and Morse,[18] Poate [23] and

13. Brewer, G. F., and Meleney, F. L.: Progressive Gangrenous Infection of the Skin and Subcutaneous Tissues Following Operation for Acute Appendicitis: A Study in Symbiosis, Ann. Surg. **84**:438, 1926.

14. Cullen, F. S.: A Progressively Enlarging Ulcer of the Abdominal Wall, Involving the Skin and Fat, Following Drainage of Abscesses Apparently of Appendiceal Origin, Surg., Gynec. & Obst. **38**:579, 1924.

15. Alexander, E. G.: Postoperative Spreading Superficial Gangrene, Ann. Surg. **84**:461, 1926.

16. Gillespie, M. G.: Phagedenic Ulceration of the Skin, Ann. Surg. **88**:248, 1928.

17. Shipley, A. M.: Progressive Gangrenous Ulceration of the Abdominal Wall, Ann. Surg. **87**:245, 1928.

18. Ballin, M., and Morse, P.: Progressive Postoperative Gangrene of the Skin, Am. J. Surg. **11**:81, 1931.

19. Lynn, F. S.: Postoperative Gangrenous Ulcer of the Abdominal Wall, J. A. M. A. **97**:1597 (Nov. 28) 1931.

20. Baker, W. H., and Terry, C. C.: A Case of Postoperative Progressive Gangrene of the Skin, J. A. M. A. **98**:138 (Jan. 9) 1932.

21. Horsley, J. S.: Certain Symbiotic Bacterial Infections Producing Gangrene with Particular Reference to the Principles of Treatment, J. A. M. A. **98**:1425 (April 23) 1932.

22. Christopher, F.: Severe Spreading Carbuncular Infection of the Chest Wall Following Rib Resection under Local Anesthesia: A Case Report, S. Clin. North America **4**:795 (June) 1924.

23. Poate, H. R. G.: Spreading Gangrenous Infections, M. J. Australia **2**:398, 1930.

Patterson [24] encountered extensive sloughing lesions of the thoracic wall following thoracotomy for empyemas.

Fortunately, in connection with Dr. William E. Lower of the Cleveland Clinic, I have had the opportunity to make careful studies of a similar case.

History.—A woman, aged 58, was admitted to the Evangelical Lutheran Hospital because of severe hyperthyroidism. After careful preoperative preparation Dr. Lower performed a subtotal thyroidectomy. Following this a consolidation of the lower lobe of the right lung developed. However, she made a rapid convalescence and was discharged on the eighteenth postoperative day.

Four days after returning home, she had a sharp, severe pain in the lower part of the chest on the right side, resulting in a pleural effusion that soon became purulent. She was then admitted to the Cleveland Clinic Foundation Hospital for a rib resection and drainage of the empyema. Pure cultures of nonhemolytic streptococci were recovered from the aspirated pus. She made such an excellent response to the thoracotomy that she was discharged on the eleventh postoperative day in spite of the fact that there was a small amount of purulent drainage from the thoracic cavity. Contrary to expectations the sinus refused to heal, though active treatment was given.

Forty-three days after resection of the rib, she complained of the wound being very painful. On examination, the skin around the ostium of the sinus was found to be hyperemic, swollen, edematous and very tender. She complained of general malaise and had a febrile reaction of 101 F. Next day the inflammatory process had extended 2 cm. beyond the sinus. The peripheral margin of the lesion was fiery red, while the tissue adjacent to the sinus was edematous and swollen and had a peculiar bluish, cyanotic tinge. Peculiarly, there was no evidence of fluctuation, and the drainage from the thoracic sinus had practically ceased. Next day the zone of reaction had extended about 5 cm.; the margins were now dark and necrotic, and the area of ulceration enlarged. Energetic local and systemic therapy was ineffective.

Six days after the onset of this local inflammation, the denuded base of the gangrenous ulcer measured 12 cm. in diameter and involved all of the cutaneous and subcutaneous structures of the right lateral wall of the chest. The base of the ulcer was clean and covered with normal-appearing muscle tissues. The border of the ulcer was formed by gangrenous cutaneous tissue that hung in loose necrotic shreds. Incision into these gangrenous areas did not cause bleeding. The edges of the ulcer were definitely undermined. The zone of reaction formed a rainbow of colors, varying from bluish black on the gangrenous areas to the fiery red in the zone of reaction and then gradually merging into the pinkish hue of normal skin.

Cultures taken from the thoracic sinus proved to be nonhemolytic streptococci, while those obtained from the advancing margin of the ulcer were nonhemolytic streptococci, Staph. aureus, diphtheroid bacilli and gram-negative bacilli. Unfortunately, no anaerobic cultures were made.

Realizing the nature of this infection, Dr. Lower excised all of the diseased tissue by means of a high frequency current. Considerable healthy tissue was sacrificed in order to get beyond the zone of the advancing inflammation. Dressings with surgical solution of chlorinated soda and the application of dry and moist heat,

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24. Patterson, H. A.: Progressive Postoperative Cutaneous Gangrene, Ann. Surg. **96**:1091, 1932.

combined with general systemic measures, resulted in a rapid recovery. The wound healed by cicatrization. It was interesting to note that the thoracic sinus stopped draining just as soon as the ulcer on the wall of the chest was excised.

COMMENT

While no attempt was made to reproduce this ulcer experimentally, I feel justified in considering the case one of infective gangrene of the skin caused by bacterial symbiosis. It corresponds in every detail to those so accurately described by Meleney.[1]

The hyperthyroidism, the thyroidectomy, the pneumonia, the empyema and the persistent draining thoracic sinus all helped to reduce the resistance of the patient to a minimum. The purulent discharge from the empyemic cavity, containing the nonhemolytic streptococci, was constantly infecting the cutaneous margins of the sinus tract. Hence the stage was all set for producing an infective gangrenous ulcer. The rapid extension of the ulcer, its destructive nature, its clinical appearance, the isolation of nonhemolytic streptococci and Staph. aureus from the peripheral margins of the lesion and its response to radical excision all substantiate the diagnosis of bacterial synergism resulting in cutaneous gangrene.

TREATMENT

Procrastination and conservatism have no place in the treatment of infective cutaneous gangrene. Delay increases the gravity of the situation. The rapid extension, the destructive nature and the toxic systemic reaction to the infections demand quick, energetic therapy. It is obvious that the type of treatment employed varies according to the nature of the provocative organisms. The therapeutic measures which are effective in controlling gas gangrene infections are impotent if applied to amebic or fusospirochetal ulcerative necrosis of the skin. Unfortunately, one cannot always wait for the laborious, time-consuming bacteriologic studies to designate the number and type of invading bacteria. In such events, the differentiation between the various forms of cutaneous gangrene depends on the appearance of the local lesion and the systemic response of the patient to those particular infective agents. Meleney has written a most comprehensive and instructive treatise on this subject.

The ideal treatment is early radical excision of the diseased tissue. Conservatism invites recurrences. The line of excision should extend well into the normal tissues, with the hope of thereby removing the advancing inflammatory process as well as the dead and necrotic structures. There is no choice between cautery and knife excision; both are effective. The postoperative therapy involves the use of hot hypertonic magnesium sulphate packs and dry heat and irrigations of the wound with an oxidizing solution. General systemic measures such as

repeated transfusions of blood, the prescription of high caloric diets rich in vitaminic content and intravenous administration of hypertonic solutions of dextrose, arsenicals, vaccines and serums have all proved efficacious in increasing the patient's defensive reactions.

Radical excision of a large gangrenous ulcer is always a mutilating procedure, particularly if it should involve the face, as in the case of noma. Fear of these resulting deformities has invited the employment of temporizing procedures. However, conservative measures fail, and the phagedenic ulceration soon produces hideous deformities that are beyond repair. Early excision minimizes the amount of tissue that must be sacrificed. The majority of deformities can be corrected by plastic surgery. No reconstructive work should be done for several months after the local infection has completely subsided. Usher and Ross [25] have reported the successful plastic repair of a facial defect caused by a destructive nomatous lesion.

Can such cases of postoperative skin gangrene be prevented? In most cases of cutaneous ulceration following suppurative operations, the wounds have been partially closed by suture. Interestingly enough, the cutaneous reaction begins around the suture, often several centimeters away from the infected draining sinus. The constant tension, combined with mechanical irritation of the suture, produces a devitalization of the local tissues, which, taking place in the presence of an infection, may initiate the gangrenous reaction. Prophylactic treatment dictates that all cutaneous wounds should be left unsutured when an intrathoracic or intraperitoneal abscess is being drained.

SUMMARY

Two cases of acute infective gangrene of the skin are presented. The first case is that of a Negro boy, aged 3, who had acute myelogenous leukemia complicated by gangrenous ulcerative stomatitis (noma), streptococcic dermatitis and bilateral bronchopneumonia. Experimental studies proved that the noma was caused by a bacterial synergism between the anaerobic micro-aerophilic nonhemolytic streptococci, the fusiform bacilli and the anaerobic Staph. aureus.

In the second case a sloughing gangrenous ulcer of the thoracic wall following a thoracotomy for a streptococcic empyema was studied. Bacteriologic, histopathologic and clinical evidence indicates that the cutaneous gangrene was caused by a symbiosis of the nonhemolytic streptococcus and Staph. aureus.

Treatment consists of early radical excision of all diseased tissue. Plastic repair of the resulting deformities can be accomplished after the infection has completely subsided.

25. Usher, S. J., and Ross, D. E.: A Case of Cancrum Oris Following Typhoid Fever with Plastic Repair, Canad. M. A. J. **25**:446 (Oct.) 1931.

LATERAL DISLOCATION OF THE WRIST JOINT

REPORT OF A CASE OF RADIOCARPAL DISLOCATION OF THE RADIAL SIDE

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The advent of the roentgenogram has added much to the knowledge of injuries of the wrist joint and has perhaps established the fact that dislocations are rare and that apparent dislocations are due to deformities produced by fracture in the region of the wrist joint.

While anterior and posterior dislocation of the wrist is met with, lateral dislocation is apparently rare. In a search of the literature we have not found a case of lateral radiocarpal dislocation. Charles Scudder, in a personal communication, stated that he did not recall having seen such a dislocation and considered it extremely rare. To his knowledge but two cases have been reported, both before the days of roentgen examination. One was recorded by F. H. Hamilton in his book "Fractures and Dislocations," published in 1884; the other was cited in the *Bulletin de la Société de chirurgie de Paris* in 1874. One was the case of a man, aged 47, who fell from a height, sustaining a compound dislocation of the left wrist and a dislocation of the elbow on the same side. F. J. Cotton of Boston informed us that he has never seen a case of lateral dislocation of the wrist. William O'Neill Sherman of Pittsburgh, in a personal communication, reported a single case with late reduction and approximately 50 per cent return of function. He expressed the belief that an immediate reduction would have resulted in a higher percentage of function.

A review of the anatomy of the wrist joint seems necessary to arrive at the mechanism of production of lateral dislocation and the constant and inconstant lesions resulting therefrom. The wrist joint is formed by the distal portions of the radius and ulna, the carpal bones and the proximal portion of the metacarpal bone. The radiocarpal joint, or wrist joint proper, is formed by the articulation of the radius with the proximal rows of the carpal, scaphoid, semilunar and cuneiform bones. The surface is concave in the anterior, posterior and lateral directions for the reception of the carpus, which contributes largely to the flexibility and stability of the wrist joint. It must be noted, however, that when the hand is held in the axis of the forearm the radius is chiefly in contact with the scaphoid and a part of the semilunar bone. The portion in contact with the semilunar bone is the inner portion or discus articularis.

When the hand is adducted or in a position of ulnar flexion the ulnar portion of the radius comes into complete articulation with the cuneiform bone and forms to some degree a fulcrum.

The intracarpal joint is formed by articulation of the first and second row of carpal bones. The arrangement of the joint does not permit lateral movement. The ligamentous structure of these joints consists of a capsular ligament common to all and extending from the articular borders of the radius and ulna to the base of the metacarpal bones. Between these attachments it connects with the first and second rows of carpal bones. It is reenforced by accessory bands, the lateral ligament being the most common. The external lateral ligament extends from the radial styloid to the base of the first metacarpal bone and is attached to the tubercle of the scaphoid and trapezium. The internal lateral ligament extends from the ulnar styloid to connect with the fifth

Fig. 1.—A drawing made at time of the first examination showing the marked deformity of the wrist joint. The hand is slightly pronated in the ulnar flexion position.

metacarpal, cuneiform and unciform bones. On the strength of these ligaments the stability of the wrist joint depends. Interosseous ligaments formed by extension of the general capsular ligament unite the individual bones. The motions of the carpal or wrist joint are flexion, extension, adduction and abduction, the major portion occurring at the radiocarpal joint.

REPORT OF CASE

On Sept. 10, 1930, J. H., a man aged 28, was admitted to the Woodlawn Hospital in a mild degree of shock as the result of an automobile accident. After the shock had been combated the following history was obtained:

While he was driving a truck under a viaduct the left front wheel hit a rather deep hole, throwing the steering wheel suddenly to the left. The wheel came up out of the hole, and hit the abutment, and the truck stopped. The patient's hands were holding the horizontal cross-bar of the steering wheel when the accident occurred.

On examination the hand was found to be swollen. There was a marked deformity at the wrist joint, part of which was due to swelling and edema of the tissues. The hand was held in a slightly pronated and ulnar flexion position. Figure 1 is a drawing made by Dr. Grimm at the time of the examination. Our impression was that there was probably a fracture of both bones of the lower part of the arm, although the carpal bone seemed to be dislocated from the radial side. There was paralysis with loss of sensation of all the fingers of the left hand except of the little finger.

The roentgen examination was made by Dr. Harry Olin and was as follows: Roentgenograms of the wrist and lower two thirds of the forearm revealed a lateral dislocation of the wrist joint toward the radial side with fracture of the scaphoid, its ulnar one half being displaced, and displacement of the cuneiform bone, both of which approximate the articular surface of the radius. In other

Fig. 2.—Lateral and anteroposterior roentgenograms taken before reduction.

words, the wrist was displaced laterally, carrying with it the ulnar half of the scaphoid and the cuneiform bone. In this position the styloid of the radius overlay the os magnum and the trapezium overlay the trapezoid. The hand was in the position of extreme adduction in the pronated position. There were several small, loose fragments of bone on the internal surface of the cuneiform bone, probably due to injury of the cortex in this region. The lateral view showed no displacement of the wrist joint either anteriorly or posteriorly. The soft tissues about the wrist were moderately thickened. Figure 2 shows the dislocation before reduction.

Under fluoroscopic guidance with manipulation, with the patient under ethylene anesthesia, the lateral dislocation was reduced by firm traction, while the hand was pulled under extension to ulnar flexion. As noted in the roentgen report, the scaphoid bone was fractured. The hand was dressed with a light anterior splint with very little pressure on the arm. Figure 3 shows the dislocation after

reduction. The scaphoid and semilunar bones were in position with slight displacement downward of the radial half of the scaphoid. The trapezium was displaced toward the ulnar side and still overlay the trapezoid, comparison being made with the right, or uninjured, wrist.

In summary, the case was one of lateral, radial displacement of the left wrist with fracture of the scaphoid and displacement of the trapezium. Reduction was accomplished in good position, but the displacement of the trapezium persisted.

Fig. 3.—Lateral and anteroposterior roentgenograms taken after reduction.

The mechanism of this dislocation is a problem. It seems clear that when the front wheel struck the hole marked adduction or ulnar flexion of the wrist was produced, and that while in this position the sudden impact of the forearm on the fixed hand with the discus articularis in contact with the cuneiform bone forced the carpal bones to a radial dislocation. The conclusions are that carpal dislocation to the radial side is produced when the hand is in extreme ulnar flexion and, likewise, that carpal dislocation to the ulnar side can be produced only when the hand is in extreme abduction. It seems evident that in

this case the capsular ligament and both the external and the lateral ligament were ruptured in the production of the dislocation.

Dr. Sherman, in speaking of the mechanism of this dislocation, said: "One can only believe that the hand was fixed on the cross-bar of the steering wheel and acted as a fixed joint, and at the moment of impact the force of the body was transferred through the arm on the diagonal, causing the external dislocation of the forearm."

When asked his opinion of the mechanism after viewing the roentgenograms, Dr. Cotton said: "I should think that it was almost impossible for it to happen after a full lateral thrust. It must have come out through a torsion strain, and my guess would be flexion and pronation, but this is purely a guess."

The roentgenograms were submitted to Dr. Scudder also. Concerning the mechanism of production he said: "I do not think one can formulate the exact forces at work in this case. The bizarre type of fracture and dislocation make one quite dizzy and certainly demand very special skilled observation and treatment."

The patient was seen several months after reduction was made. The function of the wrist was fairly good. He passed out of our hands a few days after reduction was made into the hands of an insurance company, because of the compensation law.

826 East Sixty-First Street.

PRIMARY THROMBOSIS OF THE AXILLARY VEIN

AN ANATOMIC AND ROENTGENOLOGIC STUDY OF CERTAIN ETIOLOGIC FACTORS AND A CONSIDERATION OF VENOGRAPHY AS A DIAGNOSTIC MEASURE

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AND

ELIZABETH M. McFETRIDGE, M.A.

NEW ORLEANS

Matas'[1] comprehensive study of primary thrombosis of the axillary vein makes it unnecessary for later writers to dwell at any length on the general aspects of the condition and goes far to answer his own criticism that the American literature is singularly barren of contributions to the subject. He is undoubtedly correct in his contention that even a casual survey of recent English and continental publications would increase to one hundred or perhaps more the number of cases (seventy-four) collected by Bruno Paggi in 1933. Nevertheless, the disease is unusual enough to warrant our recording two additional cases, neither of which belongs to the so-called "effort" group. We desire to report also certain studies which we have made on the living subject and on fresh autopsy material in an effort to unravel the still dubious etiology and which are not in accord with the theories heretofore advanced to explain it.

REPORT OF CASES

CASE 1.[2]—A youth, aged 19, who was in the habit of sleeping with his right arm above his head, was suddenly wakened from sleep twenty-four hours before admission by a pain which extended from the axilla down the whole arm and was associated with a stinging sensation in the finger tips. The arm had begun to swell almost simultaneously with the onset of the pain. The previous history was without importance, and the only relevant data, aside from a secondary anemia presumably due to intestinal parasites, concerned the intense swelling of the right arm and hand. The edema was of the brawny, pitting type, and the whole affected extremity was slightly colder than the left arm. The painful cord usually palpable in the axilla in acute cases of thrombosis of the axillary vein was not felt during the entire period the patient was under observation.

From the Department of Surgery of the Louisiana State University School of Medicine.

1. Matas, R.: On the So-Called Primary Thrombosis of the Axillary Vein Caused by Strain: Report of a Case with Comments on Diagnosis, Pathogeny and Treatment of This Lesion in Its Medico-Legal Relations, Am. J. Surg. **24:** 642, 1934. This article contains an extensive bibliography.

2. This case is reported through the courtesy of Dr. E. J. Richard.

A venogram made with a stabilized solution of thorium dioxide on the third day after admission showed a point of obstruction in the axillary vein distal to the first rib, with a backflow of the opaque medium into the brachial vein and as the result of the intense swelling of the extremity, a marked narrowing of all the veins visualized.

Treatment since admission had consisted of elevation of the arm on pillows and the use of a heat tent. In order to make an injection into the basilic vein it was necessary, because of the intense edema, to make a small incision over the vein. Through this incision edematous fluid promptly poured out and continued to flow profusely for seven days, at the end of which the arm was practically normal in size and appearance. The patient was discharged three days later, with instructions to return at the first evidence of any recurrence of the trouble and if no recurrence took place to report in three months. He has not been heard from since his discharge two months ago, and it is assumed that he has remained well.

Fig. 1 (case 2).—Roentgenogram showing occlusion of the right axillary vein, with formation of new collateral vessels, in a patient who had primary thrombosis of the axillary vein seven years before.

Case 2.—A woman, aged 22, exhibited large, dilated veins on the right shoulder and upper right portion of the chest, which rendered her conspicuous when she wore evening dresses. Careful questioning elicited no information beyond a history that an acute swelling of unknown origin had appeared seven years before. It had involved the whole right arm and hand and had been accompanied by pain in the axilla and arm, but it had subsided in a few weeks without active treatment. The aforementioned condition in the veins had developed gradually since that time, but there had been no further symptoms other than a slight enlargement of the arm, never more than transitory, after any unusual exertion.

Physical examination gave essentially negative results except for the slight enlargement of the right arm and the presence of large, dilated veins which coursed over the anterior portion of the right shoulder and spread out over the upper part of the chest and the breast. Venography (fig. 1) showed an obstruction in the axillary vein distal to the first rib, as in case 1, and a rather extensive collateral circulation. No treatment was indicated.

COMMENT

The history in case 1 is typical of that in the few cases reported, chiefly from the foreign literature, in which the thrombosis of the axillary vein develops in the absence of trauma. The more usual variety follows severe effort, and Gould and Patey,[3] who have reported the largest single series on record (eight cases) have outlined a composite picture of the condition from their own experience: A young man, a few hours after some unusual exercise with the right arm elevated, has pain or swelling or both, increasing in the course of the next day or two until the entire arm is swollen and somewhat cyanotic. There are no constitutional symptoms, and usually no elevation of temperature is observed. The whole arm is the seat of a solid swelling, dilated superficial veins running from the upper part of the arm to the pectoral region, and in the axilla is a firm cord, sometimes traceable to the elbow, which corresponds in position to the axillary vein. With rest and elevation of the arm the swelling slowly subsides; power of motion of the joints, which was at first limited, begins to return, and at the end of a few months normal function is fully restored except that there may be some pain when the arm is fully elevated and some permanent, usually slight, dilatation of the superficial veins on the shoulder.

The immediate cause of the accident varies widely. In the majority of reported cases there is a history of unusual effort. Schepelmann's patient sustained his injury in trying to control a wild horse; Lahaussois' and Van der Hoeven's patients fell from horses, and Austin's patient also sustained a fall. Baum's patient, a woman, had been moving heavy furniture, and Rosenthal's, another woman, had been beating clothes. Winterstein's patient, a weaver, had been piling heavy bolts of cloth on a shelf, using his left arm—it will be noted that whenever the left arm is involved the patient is left-handed or has used the left arm in some unusual manner. Schwindt's [4] patient had been pulling tents from trees, in the process of fumigating citrus trees, which involves extreme muscular effort with the arms above the head. Horton's [5] patient had dug a hole for a post with a heavy steel crowbar. The subject of Matas' detailed report sustained his injury when the wrench he was using slipped and he was thrown forward on his arm.

All these patients, it will be noted, had been engaged in some unusual, violent effort when their injuries occurred, but against their cases must be set those which followed such simple acts—"banal," as Matas calls them—as cracking a whip or even stirring a Christmas pudding. In one

3. Gould, E. P., and Patey, D. H.: Primary Thrombosis of the Axillary Vein; Study of Eight Cases, Brit. J. Surg. **16**:208, 1928.

4. Schwindt, J. K.: Traumatic Thrombosis of the Upper Extremities, California & West. Med. **27**:635, 1927.

5. Horton, B. T.: Primary Thrombosis of the Axillary Vein, J. A. M. A. **96**:2194 (June 27) 1931.

of the eight cases reported by Gould and Patey the exciting cause was not determined, but in the others the immediate causes included the playing of a game of golf, the use of an electric cutting machine, hammering, hanging curtains, lifting jars to a shelf and cleaning ceilings. The effort, in no case, seems particularly strenuous, but in nearly every case, the authors pointed out, the effort was one to which the patient was not accustomed.

The case reported by Firth and Mackay, that of a girl who stirred a pudding, is quite unusual in that a month or two after the condition had subsided in the right arm it occurred in the left arm. Equally unusual is the case reported by McGoogan and Simmons,[6] in which the thrombosis developed on the fourteenth day of an almost afebrile con-

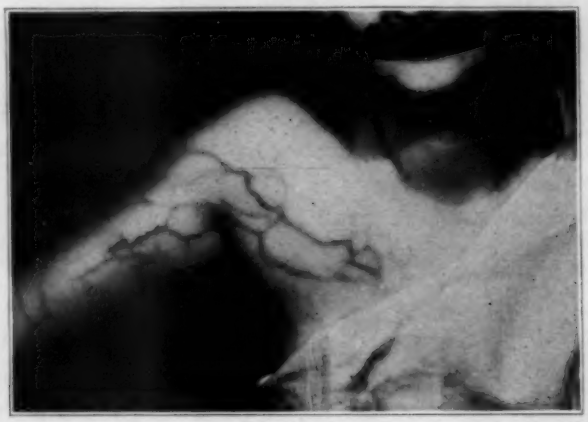

Fig. 2 (case 2).—Venous collaterals (infra-red photography) of the axillary region shown by roentgenogram in figure 1.

valescence from a cesarean section performed on a patient with nephritic toxemia. The cases in which no effort of any sort was apparent, the condition coming on during sleep, we have already commented on.

DIAGNOSIS

The clinical diagnosis rarely offers any difficulties. The characteristic features are the suddenness of onset and the rapid development of the swelling, which occurs almost simultaneously with the onset of the pain. A history of antecedent, indirect trauma can be elicited in most cases, and in most acute cases the affected vein can be palpated in the axilla as a firm, painful cord. In advanced cases the "venous ecstasies" (fig. 2), as Matas termed the collateral venous tributaries,

6. McGoogan, L. S., and Simmons, E. E.: "Effort" Thrombosis of Subclavian Vein in Puerperium, Nebraska M. J. **18**:289, 1933.

are also characteristic. The studies on the blood which have been made in a few cases do not show characteristic changes aside from that demonstrated by Horton, namely, that the oxygen content of the venous blood on the affected side is considerably less (43 volumes per cent) than on the unobstructed side (70 volumes per cent).

The differential diagnosis includes tumors, enlarged lymph nodes, fractures, arteriovenous and other aneurysms, substernal goiter, cervical ribs and other bony anomalies, regional extensions of infections, axillary phlebitis as the complication of other diseases, occasional central and peripheral neuropathic disorders, the scalenus anticus syndrome and cardiac failure. The majority of these conditions carry their own diagnosis, and confusion is unlikely. In most cases the onset is too sudden to permit the possibility that diseases of long standing, such as most of those just named, could be responsible. Roentgen examination, which has long been used to eliminate the diagnosis of such causative conditions as bony abnormalities and tumors of various kinds, should in the future, if used by the technic of vasography which will be described later in this paper, establish the diagnosis absolutely in any doubtful case, since it will determine beyond doubt the point and type of obstruction.

It is interesting that Gould and Patey reported one case, so far as we know the only one reported in connection with this condition, in which another disease was mistaken for primary thrombosis of the axillary vein. The patient presented an apparently perfectly typical picture of the condition except that it occurred on the left side, a fact which, in a right-handed subject and without any reasonable cause for the location of the trouble, should perhaps have given rise to suspicion. The edema promptly disappeared under conservative treatment, and its true origin, an aneurysm of the arch of the aorta, was not discovered until eight months later.

TREATMENT

While treatment is not our chief concern, we shall mention it briefly, partly because, in case 1 of this series, we unwittingly employed a method which improved the condition and partly because we desire to point out that vasography is also useful in setting the indications for operation.

Conservative measures, which should always be employed first, include rest, immobilization or elevation of the arm, bandaging, which gave particularly good results in Horton's case, and physical therapy. Under such treatment in ordinary cases edema is relieved, and recanalization of the vein takes place or an adequate collateral circulation develops. Matas and other authors have taken the position that when

results do not promptly appear under this system of therapy operation should be resorted to. The procedure should be either simple excision of the clot, which is ordinarily sufficient, or excision of the whole affected segment. Vascular surgery of this type is, of course, not free from risk.

Worth noting also is the case reported by Moure and Martin and quoted by Matas, in which exploration revealed an ecchymosis of the inner border of the coracobrachialis muscle. The original trouble was obviously a hematoma, which had later been absorbed, leaving a considerable collection of (sterile) serum in the intramuscular spaces. Cure was complete within three weeks after operation, and the whole case seems to bear out the suggestion of Löhr and others as to the propriety of exploration in certain cases to eliminate the possibility of extravenous pathologic changes.

In one of Wilson's [7] cases multiple incisions, about thirty in all, were made to relieve the intense edema, and this author expressed the belief that the discharge of serum by these routes initiated the improvement. Gould and Patey contended that such drastic measures are unnecessary, but it is interesting to recall that in one of our own cases, in which the thrombosis was observed in the acute stage, the same treatment was unwittingly administered, as we have already noted, and prompt improvement followed the profuse discharge of serum through the incision made for the purpose of introducing the opaque medium.

Venography, in our opinion, can be utilized for determining the indications for operation: It settles absolutely, as we have already pointed out, the question of whether obstruction exists and whether the condition is of intravenous and extravenous orgin, and in most cases the answer also settles the question of whether surgical intervention would be helpful or useless.

PROGNOSIS

We cannot agree with authors who state that the prognosis is uniformly good. For life it undoubtedly is. In none of the reported cases did the patient die of the accident—although one or two died of other diseases associated with it—except in the case reported by Moure and mentioned by Matas with the comment that the patient's condition does not properly belong in the classification under consideration. In that case all the facts were opposed to a diagnosis of primary thrombosis of the axillary vein: The patient, a 70 year old woman, died, four days after sustaining a fracture of the neck of the humerus, from an embolus which was proved at autopsy to have originated in the subclavian vein on the same side as that on which the fracture occurred. In only one

7. Wilson, G.: Brachial Monoplegia Due to Thrombosis of the Subclavian Vein, Am. J. M. Sc. **163**:899, 1922.

authentic case did embolism occur, and in that instance Schepelmann explored the affected area and removed the clot.

In many cases prompt improvement follows conservative treatment, or even occurs without treatment, and there is no recurrence. In other cases, as in case 2 of this series mild residual symptoms are noted over many years. In still other cases there is a recurrence whenever the person endeavors to resume his former occupations, and the accident assumes, as Matas points out, a medicolegal aspect. This happened in the case which forms the basis of his own extensive study, and in the case reported by Jeanneney and Mathey-Cornat recurrences persisted for six years, or until the whole affected segment was excised.

THEORIES OF ETIOLOGY

Before passing on to our own investigations as to the origin of primary thrombosis of the axillary vein it is necessary to mention briefly the theories formerly or presently held, many of which predispose one to agree with Shoemaker, who said in discussing Schwindt's case, that the whole state of thrombosis is so inexplicable that it should perhaps be regarded simply as an act of God. The suddenness of onset, as we have already intimated, seems to indicate that none of the aforementioned predisposing causes is an important factor, for the factors which precipitate the attack are entirely inconstant. Wilson attributed his first case to tuberculosis and the second to syphilis, but the mere reading of his report establishes the fact that both these factors were coincident rather than causative. Lowenstein [8] was probably right in saying that syphilis as a cause was invoked in that case and in others merely for the reason that it is invoked in any poorly understood case. Ruge's contention that the thrombosis might be the first sign of a latent cardiac condition may be promptly dismissed, for there is nothing in the clinical course of any reported case to support such a theory. The acts and positions which precipitate thrombosis of the axillary vein are done so often and assumed so frequently by so many persons, in so much more exaggerated a fashion than that which precipitates the attack, that if they alone were responsible the disease would be frequent rather than, as it is, infrequent. In certain cases, as in that of the patient operated on by Moure and Martin, quoted by Matas, an extravascular cause seems to be operative, perhaps the rupture of muscle fibers with consequent obstruction of the vein by external pressure produced by a hematoma or by an accumulation of serum, if not by both. McGoogan and Simmons suggested a similar origin for the condition in their own

8. Lowenstein, P. S.: Thrombosis of the Axillary Vein, an Anatomic Study, J. A. M. A. **82**:854 (March 15) 1924. This article contains an extensive bibliography.

case; their idea was that the thrombosis was produced by the patient's pulling herself up in bed during her convalescence. But again, if such a factor were a constant cause, a large number of convalescent persons would unquestionably exhibit the disease.

The infectious theory, as Matas pointed out, naturally arises in any thrombotic condition, but both clinical and bacteriologic evidence oppose it. Of twenty-seven cases in which operation was performed, data as to bacteriologic findings are available in only seven; the findings were positive in three, it is true, but in each of these cases there was definite evidence of a septic phlebitis in the vessel wall, a finding which is not in accord with the clinical history and termination in the great majority of cases. In Matas' opinion the "infectious traumatic phlebitis" theory of the French school is an unwarranted and untenable assumption.

Matas showed an inclination to give much more weight, however, to the sympathetic theory recently advanced by Cottalorda, on the basis of operation in his own case, which revealed not a thrombus but a rigid spasm of the vessel wall. The theory, to state it briefly, is that the vascular lesion originates in a venous spasm induced by sympathetic irritation, which in turn is the result of trauma. The thrombus is a possible but not an essential part of the picture. This view, Matas stated, is quite in accord with the theories of Leriche, who expressed the belief that venospasm is the effect of the vasomotor reflexes which originate in the perivenous sympathetic nerve fibers.

The close relationship between the vascular system of the axilla and the nerve distribution in this area makes it not unreasonable, as was pointed out by Wexberg, of the department of psychiatry of the Louisiana State University School of Medicine, in a recent discussion of this condition, that some neurologic factor may later be found to be of considerable importance. It will be remembered that the axillary vein lies on the medial side of the axillary artery, partially overlapping it, and that between the two vessels lie the medial cords of the brachial plexus, from which spring the median ulnar and medial anterior thoracic nerves. In Wilson's case, in which a paralysis of the arm was associated with the thrombosis of the axillary vein, the paralysis was undoubtedly due to the pressure of the obstructed vein on the brachial plexus.

Von Schrötter, who reported the first case in 1884, although the condition had unquestionably been described by Sir James Paget nine years earlier, expressed the belief that the thrombosis originates in a sudden stretching and compression of the vein after an effort, which produces a localized phlebitis with consequent damage of the vessel wall. Cadenat, who collected data on twenty-seven cases in 1920, considered the cause to be a venous dilatation and stasis due to expiratory effort, combined

with injury to the endothelium of the venous tributaries at their junction with the axillary vein as the result of a single or of repeated muscular strain. Willan suggested that the condition results from trauma to the head of the humerus, and also advanced the idea, which has been more or less widely held ever since, that the axillary vein suffers damage from the outer border of the first rib during vigorous exercise with the arm in the abducted position.

Schwindt, in an extensive study of thrombosis, quoted Welch to the effect that the factors which govern the slowing of the blood stream in the veins, supposedly the underlying factor in all thrombotic states, include "flow from the smaller into larger channels, presence of valves, and fixation of the venous wall in certain situations to fascia and bones," all of which factors are embraced in a striking combination in the venous supply of the shoulder girdle. Schwindt pointed out that the axillary subclavian vein is large and has several valves and several small tributaries and that there is a fibrous attachment to the costocoracoid ligament, to the clavicle above and sometimes to the rib below. He then referred to the arguments of Rosenthal and Pellows: When the arm is elevated, intrathoracic pressure or expiration is directed outward, through the subclavian vein, and unusual muscular contractions about the veins in the arm direct the peripheral force inward through the axillary vein, the meeting of these opposing forces under the clavicle producing a slowing of the stream at the precise point where the vein presents all the anatomic peculiarities which Welch considered competent to induce thrombosis.

Piccagli,[9] the latest writer on the subject, expressed the belief that the anatomic relations of the axillary vein and its tributaries in the region of the costocoracoid membrane are the chief factors and that in his own case the forceful muscular contraction may have torn the wall of the vein, with resulting injury to the intima. Taylor,[9a] in reporting two cases of thrombosis of the subclavian vein, with probable involvement of the impalpable portion of the axillary vein, both in patients who engaged in rowing, pointed out that in neither of these cases could the position of abduction have played any part, since that position is not assumed in rowing. Taylor placed the responsibility in these two cases on the final maneuver in the stroke, which introduces the position of adduction, but it should be noted that that factor does not enter into any other reported case. In support of his theory he mentioned that Appleton, of the Cambridge School of Anatomy, demon-

9. Piccagli, G.: Traumatic Thrombosis of the Right Axillary Vein, Chir. d. org. di movimento **19**:186, 1934.

9a. Taylor, C. H. S.: Primary Thrombosis of Subclavian Vein, Brit. M. J. **2**:818 (Nov. 4) 1933.

strated to him that by a certain downward motion of the shoulder, with the arm hanging, which simulates the final motion of rowing, the subclavian or axillary artery, and presumably the corresponding vein also, could be so compressed as to stop the radial pulse. Since the axillary vein ends at the outer border of the first rib, Taylor added, it is not subjected to bony presssure as is the subclavian vein, and he thought it possible, that thrombosis of the axillary vein actually originates in the subclavian vein.

However much they may differ as to the how and wherefore of the mechanism, all recent students of thrombosis of the axillary vein agree that trauma, plus some anatomic predisposing cause, is the responsible factor. Lowenstein, who was the first to attack the subject from any but a theoretical point of view, made dissections of the axillae of thirty cadavers and studied transverse and sagittal sections of six additional bodies. As the result of this study he advanced the following theory: The axillary vein is distended by the abduction or extension and lateral rotation of the arm. Venous stasis or circulatory slowing is brought about by the forced expiration that accompanies effort. Under these circumstances pressure on the vein by the costocoracoid ligament, furthered by the subclavius muscle, is sufficient to bring about changes in the vascular endothelium which are, in turn, sufficient to cause thrombosis of the axillary vein.

Gould and Patey, continuing Lowenstein's work, injected plaster of paris into the axillary veins of cadavers with the arm in the abducted position. In two instances they observed broad, deep grooves from the pressure of the subclavius muscle, and in another, a shallow groove corresponding to the position of the costocoracoid ligament. In still other dissections they noted that a practically constant anatomic feature of the vein at the level of the subclavius muscle was the presence of a competent bicuspid valve which was so placed that the pressure of the muscle stretched the wall of the vein in the long axis of the valve. The valve cusp, regardless of location, is always a delicate structure, composed only of a thin sheet of fibrous tissue covered on either side with endothelium. Gould and Patey's theory is that the pressure of the subclavius muscle is responsible for trauma to the vein and that rupture of the delicate subclavio-axillary valve is the fundamental pathologic lesion, while the position of abduction and the expiratory effort resulting in distention of the vein are predisposing factors.

None of these theories, it will be noted, explains why, if a common anatomic factor is responsible, the condition does not occur more often, and some of them do not stand up in the face of the evidence. Gould and Patey's theory, for instance, that the primary lesion is in the subclavio-axillary valve, is overthrown by the fact that in the cases in

which surgical intervention has been practiced, the position of the thrombus is not constant. The one thing that would settle the dispute, a careful autopsy on an affected subject, is lacking, and Wilson was quite right in regretting that in his first case, in which necropsy was performed, entire attention was concentrated on the obvious thoracic condition, tuberculosis, and the affected vein was not dissected. It seemed to us questionable that dissections on prepared cadavers, however carefully they may be made, are exactly comparable to such dissections on fresh material, and we decided to undertake an investigation with such material and to combine it with a study in the living subject by means of

Fig. 3.—Roentgenogram of normal basilic and axillary veins, showing valves of the veins.

venography with thorotrast [10] (stabilized thorium dioxide solution), the use of which in the two cases which had come under our observation had been helpful.

NEW DATA

Stabilized thorium dioxide solution (thorotrast Heyden) is an opaque medium of practically the same viscosity as blood and miscible with it,

10. Thorotrast is not acceptable to the Council on Pharmacy and Chemistry of the American Medical Association. A preliminary report appeared in the Journal of the American Medical Association of Dec. 24, 1932, p. 2183.

but of a higher specific gravity. Its toxicity is negligible, and we have used it for the last two years, without ill effects of any sort, in a study of peripheral vascular disease. There seemed to be no reason, therefore, for not using it in the first case of thrombosis of the axillary vein which we observed, and for not continuing its use thereafter. At first thought, it might seem somewhat unsafe to inject a foreign substance into the vein in a case of suspected thrombosis, but the amount

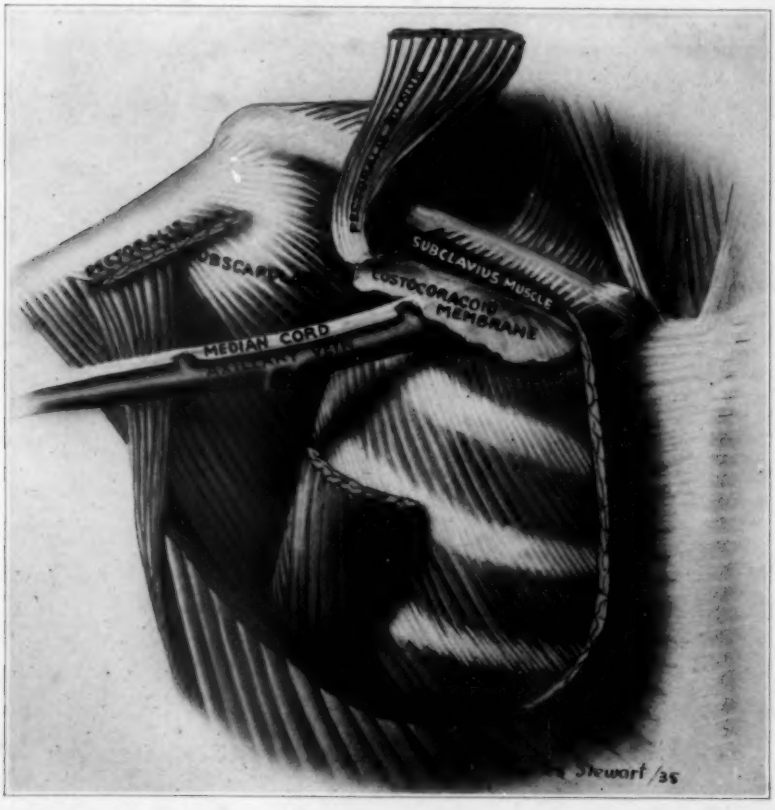

Fig. 4.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is held at an angle of 45 degrees to body.

used is so small, never exceeding 5 cc., and the injection is given with so little pressure that the risk of disturbing the thrombus is academic rather than real. In the normal subject, on whom all our later studies were made, injection of 5 cc. of thorotrast into the basilic vein outlines that vein and the axillary and subclavian veins and, occasionally, the upper part of the superior vena cava and some of the venous tributaries as well (fig. 3).

Before proceeding to a discussion of our findings in these cases, it is necessary to recall certain points of anatomy (fig. 4). The axillary vein is a continuation of the basilic vein and extends as such from the lower part of the teres major muscle to the outer border of the first rib, at which point it becomes the subclavian vein. Thence it continues to the sternal end of the clavicle, where it unites with the internal jugular vein to form the innominate vein. Its tributaries include the brachial vein, which flows into it near the lower border of the subscapularis muscle, the cephalic vein, which flows into it near its termination, and other tributaries corresponding to the branches of the axillary artery and including the thoracic, thoraco-acromial, lateral thoracic, posterior subscapular and posterior and anterior circumflex veins.

The axillary vein passes over the subscapularis muscle, which is attached to the head of the humerus at the lesser trochanter, and under the pectoralis minor muscle. As it passes over the first rib to become the subclavian vein it is covered by the costocoracoid membrane and ligament and the subclavius muscle. Its relation to the regional nerves has already been mentioned.

The anatomic points which we have just outlined can be clearly demonstrated in a normal subject by injecting thorotrast into the basilic vein by the technic already described (fig. 3), the exposure being made on a 14 by 17 inch (35.56 by 43.18 cm.) plate just as the last cubic centimeter of the solution is injected. The anatomic relationship immediately changes, however, when the factor of movement is introduced, as we were able to prove by further roentgen studies with this medium. The vein, being only loosely attached to the surrounding structures, can accommodate itself to moderate changes in position without undergoing material alteration in size. On the other hand, when the arm is hyperabducted and externally rotated the relations between the vein and the subscapularis and the relations between the vein and the head of the humerus are immediately altered (fig. 5).

In the position of hyperabduction and external rotation, as the subscapularis muscle comes to lie between the vein and the head of the humerus, there is a compression of the vein as it passes over it that is entirely absent in the position of internal rotation. Again, when the arm hangs by the side the vein is widely separated from the head of the humerus, but as the position of abduction and external rotation is assumed, it approaches closer and closer to it. The scapula and clavicle are elevated; the muscles attached to the shoulder girdle are put on a stretch, and the axilla becomes a flattened instead of a pyramidal surface.

As a result of these changes the axillary vein is also elevated and held in the new position, in close approximation to the subscapularis muscle near its insertion into the lesser trochanter of the head of the humerus, the compression already described occurring as the complete position of abduction and external rotation is assumed.

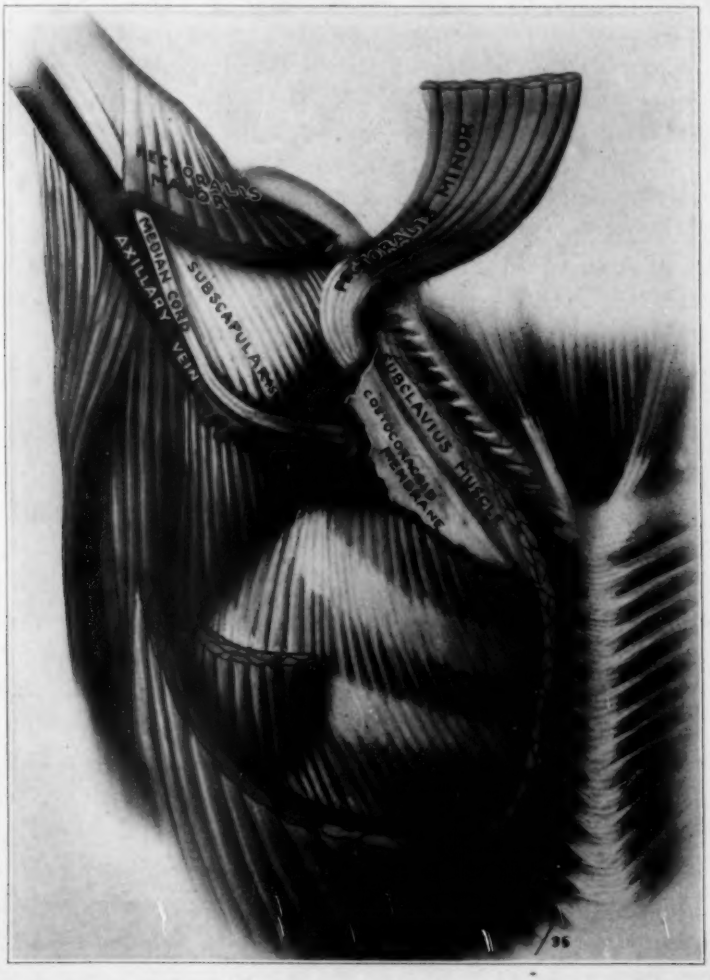

Fig. 5.—Drawing illustrating anatomic relations of parts of the axillary region when the arm is in a position of hyperabduction and external rotation. Note the constriction of the axillary vein against the subscapularis muscle and the stretching of the vein just proximal to the point of constriction.

By roentgen evidence (fig. 6) the obstruction hitherto assumed to occur over the first rib is actually not at that site but rather at the point at which the vein passes over the subscapularis muscle in the position of

hyperabduction and external rotation, and this fact we also established by the dissection of fresh autopsy material. It is true that as the vein crosses the first rib it is more oval than it normally is, and slightly flattened, but a true constriction is not present, nor could we detect any material alteration in the actual venous diameter. We assume, therefore, that Lowenstein's and Gould and Patey's observations, which are contradicted by our own findings, differ from them because they were made on fixed instead of on fresh material.

Fig. 6.—Roentgenogram showing point of constriction of the axillary vein below the head of the humerus against the subscapularis muscle in a position of hyperabduction and external rotation.

The stretching of the vein, which several theories assume as the responsible factor in thrombosis of the axillary vein, was also studied in fresh autopsy material. The vein was exposed without disturbing the subclavius muscle, and care was taken to preserve as much as possible of the costocoracoid membrane and the costocoracoid ligament. Then, with the arm raised at an angle of 45 degrees to the body, the course of the

vein was outlined by means of small pins placed at equal distance from each other, and its length was measured, this measurement being compared with a similar measurement taken later under the same circumstances, but with the arm externally rotated and hyperabducted. The only part of the vein found to have stretched was the portion just proximal to the head of the humerus and just proximal also to the point at which in our roentgen studies constriction had been observed. In the subject under observation the variation in the length of the vein in the two positions was 0.8 cm.

We then proceeded to study the effect on the rate of the blood flow and the venous pressure by the constriction and stretching which we had observed in the axillary vein in the position of hyperabduction and external rotation. The first observation was made with the fluoroscope, after the vein had been visualized with thorotrast. In three patients the emptying time, that is the time required for all the solution to be washed out of the vein, so that it was no longer visible under the fluoroscope, averaged three and a half minutes when the subject was in the recumbent position and the arm was placed at an angle of 45 degrees to the body. When an additional amount (5 cc.) of the solution was injected, after the vein was completely empty, and the arm was immediately hyperabducted and externally rotated, this being the position in which the constriction and stretching of the vein had been noted, there was an almost immediate emptying of the vein, which at the end of thirty seconds showed none of the solution in the part proximal to the point of constriction. It is obvious, then, that instead of a slowing of the venous current occurring in this position, which was previously believed to take place, the emptying time is actually faster than in the approximately normal position of the arm at an angle of 45 degrees to the body.

We passed on, finally, to the question of the venous pressure, the first observation being made with the fluoroscope after injection of thorotrast, with the arm at an angle of 45 degrees to the body. We noted that in this position there was on each normal inspiration a backflow of the opaque solution through the axillary vein and that on coughing or straining this backflow was so much exaggerated that the solution passed backward into the vessels of the arm.

The venous pressure in normal subjects was then measured with the arm in the same position and was found to be just sufficient to force the blood backward through a no. 20 needle, without any overflow. The arm was then raised to a position of hyperabduction and external rotation, a glass tube measuring 100 mm. in length, and of the same bore as that of the needle, having been previously attached to the needle.

This movement was found to cause a rise of about 20 mm., which was, however, momentary, though when the patient coughed or strained the pressure was markedly increased, the blood in some subjects actually overflowing the tube. From these observations it appears that the important factor in raising the venous pressure is not the position of the arm, but rather the increased thoracic pressure which is caused by coughing or straining.

It is, of course, possible that the stretching of the vein which was demonstated in our fresh autopsy material may cause some damage to the intima of a valve or a tributary, particularly if some anomalous distribution of the tributaries should be present, but this does not seem reasonable. In the four patients whose axillary veins were punctured in our study of the venous pressure there was no clinical evidence of any clot or occlusion following the trauma. Although we found no venous or muscular anomalies in the subjects we observed, such anomalies are notoriously frequent, as Lowenstein has pointed out, and it may be that they are present in the patients in whom thrombosis of the axillary vein occurs. Again, the lack of autopsy material in such cases precludes categorical statements.

CONCLUSIONS

Indeed, the conclusion of the whole matter seems to be that some individual variation is the final cause of the accident. James made that point in the discussion of his two cases of thrombosis of the subclavian vein and expressed the belief that this idea of an "idiosyncrasy of anatomic structure" is supported by the fact that nearly all reported cases are observed in right-handed male subjects, in whom the accident occurred through traumatic pressure or pinching of surrounding structures of more than ordinary development. The results of the roentgen and autopsy studies we have reported seem to us to be sufficiently substantiated to be accepted, even though they contradict the results of previous work that has been done. They prove clearly that the constriction of the vein occurs, not as was previously believed over the first rib beneath the subclavius muscle, but below the head of the humerus and against the subcapsularis muscle. The stretching of the vein, the occurrence of which has heretofore merely been assumed, takes place, we have shown, only within the part of the vein just proximal to the point of constriction below the head of the humerus. We have shown that instead of the slowing of the venous current which has previously been assumed to occur, the emptying time is actually more rapid in the position of hyperabduction and external rotation than when the arm is held at an angle of 45 degrees to the body. Finally we have shown that the increase in the venous pressure which has always been

accepted as a causative factor is brought about not by the change of position in itself but only when the additional factor of strain or effort is introduced.

It must be emphasized again, however, that the problem is in no wise solved by the facts we have brought out. The anatomic and physiologic factors we have demonstrated serve merely as contributing causes. Until adequate autopsy material on patients with thrombosis of the axillary vein is available the etiology of the condition must remain speculative, though the most reasonable assumption is that the constant underlying factor is some individual anatomic variation.

Fig. 7.—Roentgenogram showing occlusion of the axillary vein by metastatic carcinoma of the axillary lymph gland. Note the backflow into the cephalic and collateral vessels.

OTHER USES FOR VASOGRAPHY

In conclusion we wish to report that in addition to the two cases of primary thrombosis of the axillary vein we have studied by this method, we have also studied four cases of occlusion of the axillary vein caused by tumors of the axillary lymph nodes. In all the latter cases (fig. 7) we were able to demonstrate the site of occlusion and the collateral circulation which had developed after occlusion had occurred. The obstruction is evident as a blockage of the opaque medium, which may flow back into the brachial or even into the cephalic vein. It

seems to us that in cases of malignant involvement of the breast this method should prove valuable in demonstrating the presence of metastatic lymph nodes while they are still impalpable. It may also be of value in demonstrating the presence of mediastinal tumors and other occlusions of the vena cava which cannot be seen by the ordinary roentgen or fluoroscopic examination.

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CLINICAL STUDY OF THE SPERMATOGENESIS OF UNDESCENDED TESTICLES

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This paper is based on a study of a group of patients with either unilateral or bilateral undescended testicles observed at the Children's Hospital, from 1900 to 1934. During this period 665 cases of cryptorchidism were observed in this clinic. Unfortunately, 186 of the patients have disappeared so that all efforts to reach them over a three year period have failed. Of the remaining 479, 336 have been located, interviewed and examined. Larger series than this have been reported from other clinics, but so far as can be determined all of the investigators have judged the excellence of their end-results on the position and size of the testicle at periods varying from two months to several years after operation. These investigations have been valuable for comparing the various methods of orchiopexy to place and hold the testicle in the scrotum. However, the prime interest in these cases should be centered not on the cosmetic result but rather on the fertility of the patient or the relative fertility in comparison with that of normal persons. The problem of fertility of these persons with cryptorchidism has thus become the basis of this investigation in an effort to throw some light on the spermatogenesis of the testicle for which an orchiopexy has been performed. Naturally, investigations of fertility are impossible until early adult life, so the number of persons available for study in this group of 336 was limited. The present review, which represents only a preliminary report of this work, is based on studies on the fertility in 89 cases from ten to thirty years after operation.

Before considering the fertility of the patient on whom orchiopexy was done one might first review [1] what has been learned and generally accepted about the spermatogenesis of the testicle that remains outside of the scrotum. Experimentally it has been shown in animals that a testicle placed in the abdominal cavity shows evidence of degeneration, but if it is replaced in the scrotum before complete degeneration occurs it will again become apparently normal. If allowed to remain in the abdomen the procreative power of the testicle is lost. It has been shown that testicles removed before puberty, though such instances have been

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1. Wangensteen, O. H.: The Undescended Testis, Arch. Surg. **14**:663 (March) 1927.

few, have been similar in appearance whether they were undescended or not. The undescended testicles that have been removed during the first two to three years after puberty have shown beginning degeneration but with spermatocytes and spermatozoa still present. The greater percentage of retained testicles that have been removed from adults have shown principally the loss of germinal epithelium from the seminiferous tubules and complete absence of spermatozoa. It has thus been generally but not universally accepted that if the undescended testicle is to have spermatogenic power it must be placed in the scrotum before puberty. That this is not always a necessity is shown by the reports of a few isolated instances of fertility in persons with complete cryptorchidism.[2] It has been estimated by one investigator [3] that as high as 10 per cent of undescended testicles show some spermatogenesis. It thus becomes of importance, in order to justify operative procedures in these cases, to prove that in more than 10 per cent of the patients on whom orchiopexy is performed there is fertility and likewise to prove not only the mere presence of spermatozoa but their presence in large enough number to make progeny possible.

Certain operative and nonoperative procedures are available for insuring placement of the testicle in the scrotum. One group advocates leaving the testicle entirely alone in the belief that eventually it will descend into the scrotum before or at the time of puberty. It is impossible to conceive how any one can hold to this theory in all cases. One must encounter at some time the firm, fibrous tissue adhesions of the cremasteric muscle to the structures of the cord, the fibrous tissue blocking the entrance to the small, underdeveloped scrotum, or the testicle that has been reflected upward from the external ring and held in this position by the insertions of the abnormal gubernaculum or adhesions of the associated hernial sac. It is rather incongruous to suppose that at some time in development this fibrous tissue will suddenly disappear and allow the testicle to drop like a plummet into the scrotum. Nevertheless, there is one type of so-called undescended testicle that will descend unaided into the scrotum. This occurs in patients who have an extremely active or short cremasteric muscle. It is not associated with a hernia, and the testicle usually can be brought into the scrotum by manual traction. When traction is released the testicle again recedes into the inguinal canal. The scrotum is better developed in these patients than in those in whom the cord is congenitally short. Therefore it becomes apparent that if the testicle can be

2. Maréchal, A.: Thèse de Paris, no. 307, 1887; quoted by Wangensteen.[1] Taylor, A. S.: Manual of Medical Jurisprudence, Philadelphia, Lea Brothers & Co., 1886; quoted by Wangensteen.[1]

3. Uffreduzzi, O.: Dei Pathologie der Hodenretention, Arch. f. klin. Chir. **100**:1150; **101**:150, 1913.

brought into the scrotum at all it may conceivably descend of its own accord. Of 336 cases in which there has been a periodic follow-up this has been demonstrated to be true in 21. In the same group of 336 cases there were 26 patients on whom an orchiopexy was never performed. In these 26 the testicles could not be brought into the scrotum on the initial examination. In each case the testicle remained in its original position or atrophied to such an extent that it could not be palpated in the inguinal canal.

It thus becomes apparent that the majority of patients need surgical assistance for the proper placement of the testicle. There are four main principles of operative treatment.

Orchidectomy is the procedure reserved for those cases of unilateral nondescent in which the testicle cannot by any method of orchiopexy be placed in the scrotum. In many clinics it is thought to be wiser to remove the testicle rather than to allow it to remain high in the inguinal canal, where it is subject to trauma and causes discomfort. It must also be remembered in this regard that the undescended testicle is more likely to show malignant change than is the normally descended testicle.[1] If the testicle cannot be placed low in the inguinal canal or in the scrotum, where malignant change may be readily noticeable, it is perhaps better to remove it. However, removal should not be done before the patient is 16 or 17 years of age unless the testicle seems to be markedly atrophied before that time. The interstitial cells which supposedly produce the testicular hormones that are linked with the development of the secondary sex characteristics are not destroyed unless the testicle is completely atrophied. If there is any question that the development of the secondary sex characteristics might be retarded owing to the removal of the seat of these hormones it would then seem wiser to attempt orchiopexy rather than orchidectomy on each patient under the age mentioned. If for some reason the testicle cannot be brought down into the scrotum, it should be left in situ, and orchidectomy should be performed at a later date.

The second type of repair is based on the theory that the artery of the vas deferens supplies enough blood to the testicle so that the other vessels of the cord may be cut without impairment to testicular growth. As the vessels are usually the shortest structures of the cord in persons with undescended testicles, proper patience may be lacking to free these structures so that they can be stretched the necessary distance for the testicle to be placed in the scrotum. In every patient in the clinic of the Children's Hospital in whom the vessels were cut the testicle could easily be placed in the scrotum, where it remained without retraction. However, from ten to twenty years after operation every one of the patients treated in this fashion showed

complete atrophy of that testicle. This proves that it is not a desirable operation; in this clinic the result has been poor in every instance.

The third principle of repair comprises freeing of all adhesions of the cord, division of all the cremasteric fibers and freeing of the vessels and vas deferens from the posterior portion of the peritoneum by dissection through the internal inguinal ring. If only the vas deferens and the main arterial and venous trunks are left the cord is usually of sufficient length so that the testicle may be placed in the scrotum without tension. Usually a purse-string suture is placed at the neck of the scrotum to prevent possible retraction. It is to be remembered that this method of repair is based on the theory that with sufficient perseverance the cord can be lengthened. It is thought that to hold the testicle in the scrotum under tension, if lengthening is not adequate, cuts off the blood supply and leads to eventual atrophy. This method of repair, then, does not include fixation of the testicle in the scrotum in any way except perhaps by a temporary stitch to be removed at the end of the operation. It might be said here that this is the type of repair that has been used almost as a routine in the Children's Hospital.

The fourth method of surgical treatment combines the freeing of the cord with fixation of the testicle in the scrotum. Into this division falls the Torek operation and all its modifications. If the Torek operation is used as Torek originally described it (i. e., to free the testicle without injury to the main vessels until it can be placed in the scrotum without tension and then to sew it to the thigh), this fixation becomes effective in aiding the stretching of the underdeveloped scrotum and in preventing retraction of the testicle from scar contracture in the wound itself. It is the opinion in the clinic of the Children's Hospital that if the testicle can be placed well within the scrotum without tension fixation is unnecessary. However, this Torek procedure might well be used in those cases in which in spite of all possible lengthening the testicle will reach only to the upper limit of the scrotum. Such mild traction produced by the Torek procedure in these cases perhaps does impair but does not completely shut off the blood supply. In the modifications of the Torek procedure the tunica or the gubernaculum but not the testicle is usually included in the fixation stitch, and thus further testicular trauma is avoided.

One recent investigator [4] has estimated that there are over forty different operations described to place the testicle in the scrotum. All these methods represent minor variations of the four principles that have been described. It now remains for further investigators in this field to show which of these various methods results in production of

4. Wolfson, W. L., and Turkeltaub, S. M.: A Modified Torek Operation, Am. J. Surg. **25**:495, 1934.

the highest degree of fertility for the patient. However, before discussion of the fertility of persons with this abnormal condition it may be well to review a few of the known factors affecting the fertility of the normal person.

From recent reports it has been shown that the semen of the normal male contains between 100,000,000 and 120,000,000 actively motile spermatozoa per cubic centimeter.[5] Studies of the head, neck and tail of the sperm have revealed that between 8 and 10 per cent may be abnormal in size and shape.[6] Fertility is thought to be greatly impaired if the percentage of abnormal forms reaches 25. Considerable variation from these normal figures is reported in the same person, depending on age, exercise, diet, mental strain, fatigue, the activity of the endocrine glands and, occasionally, the frequency of sexual intercourse. It is thus apparent that one count of the sperm may give a false interpretation of the fertility of that person, as the count in one person has been known to vary from 50,000,000 to 200,000,000 sperm per cubic centimeter during a period of observation. However, unless there is some real pathologic process present the count does not usually go below 50,000,000 sperm per cubic centimeter. It has been generally considered but not definitely proved that an unvarying count of 25,000,000 sperm per cubic centimeter represents the minimum number necessary for fertility, as usually that many spermatozoa are estimated to be destroyed by the vaginal secretions. Instances of proved fertility in persons with counts lower than 25,000,000 per cubic centimeter have been reported,[5a] and the occurrence of such cases is confirmed by this investigation.

METHOD OF STUDY

In the study of persons with cryptorchidism, the same technic in making the counts was employed as that advocated by Macomber and Saunders.[5a] The specimens of semen were collected either in a condom during intercourse or in a Petri dish during masturbation. In every instance possible a collection was made by both methods. It was found that the counts of both specimens were almost identical. The counts were made exactly as a white blood cell count except that sodium bicarbonate was used as a diluent, and the total was computed on the basis of a cubic centimeter rather than of a cubic millimeter. Because of the uneven distribution of spermatozoa in the collected specimens three dilutions and counts were made on each specimen, and the results were averaged. Even this did not make the counts absolutely accurate, but they more nearly approached a mean. In all cases of abnormally low or high counts, specimens were collected over a period of time and the results were averaged. In all instances a careful sexual

5. (*a*) Macomber, D., and Saunders, M. B.: The Spermatozoa Count, New England J. Med. **200**:981, 1929. (*b*) Belding, D. L.: Fertility in the Male: II. Technique of Spermatozoa Count, Am. J. Obst. & Gynec. **27**:25, 1934; (*c*) Fertility in the Male: I. Technical Problems in Establishing Standards of Fertility, ibid. **26**:868, 1933.

6. Moench, G. L.: Am. J. Obst. & Gynec. **25**:410, 1933.

history was taken so that if extremely low counts were found due consideration and treatment might be given to any factors that might influence the count.

These determinations of spermatozoa were carried out on all the married and unmarried patients over 20 years of age who could be located. Because the investigation involved consideration of an infirmity to which many of them were sensitive it was difficult to persuade them to come in for an examination. The 89 persons on whom studies of fertility were conducted constitute a group made up of 20 persons with complete cryptorchidism and 69 with unilateral cryptorchidism.

OBSERVATIONS

The patients with bilateral nondescent of the testicles constituted the most important group for the study of spermatogenesis. It is obvious that no definite conclusions can be drawn from a series of only 20 persons. Interpretation of the results is difficult in a number as limited as this, but it is hoped that this study will stimulate further work in other clinics, so that by grouping the results a true evaluation may be reached.

Of the 20 patients 2 were seen in the clinic and operation was advised but not performed. One was seen at 11 years of age. At that time he had bilateral inguinal hernia, a small left testicle in the inguinal canal and a right testicle of normal size also in the inguinal canal. Orchiopexy was never performed, but a right herniorrhaphy was performed at the age of 20. On examination the patient was 41 years of age. Examination revealed both testicles to be small but in the scrotum, apparently having descended unaided. The patient was married and had three normal children. The other patient was seen in the clinic at 6 months of age. At that time neither testicle could be felt and no hernial sacs were found. At the age of 12 the patient had severe poliomyelitis, which greatly deformed his entire body. At examination the man was 28 years of age and was unmarried. Examination of the testicles revealed that they were normal in size and sensation, but the right one remained low in the inguinal canal while the left was low in the scrotum. The count of spermatozoa was, however, 45,000,000 per cubic centimeter. This is adequate for fertility but is much less than that found in the normal person. It is questionable whether this patient ever had a true cryptorchidism. Examination of the testicles in infancy may be difficult owing to the overactivity of the cremasteric muscle, which on the slightest stimulation may pull the testicle back into the inguinal canal.

There were 3 more patients in the group with bilateral undescended testicles who were seen in the clinic during childhood but were operated on at neighboring hospitals. In 1, examination at 5½ years revealed the left testicle situated in the inguinal canal and the right testicle inside the internal ring. He was operated on at the age of 13, when a left orchidectomy and a right orchiopexy were done. At the time of recent examination the patient was 29 years of age. Examination revealed a man normal in build and development. The left testicle was absent; the right was of normal size, very sensitive, of good tone and in the scrotum. The patient had been married nine years and had no children. No contraceptives were used at any time. The patient had had no venereal disease. Repeated examination of the semen revealed no spermatozoa. The second patient, seen first at the age of 8½ years, had bilateral inguinal hernia and testicles that could be palpated in the inguinal canal but could not be brought into the scrotum. An orchiopexy on the right side was performed in the clinic of the Children's Hospital. The testicle later retracted so that at the age of 14 a second orchiopexy on the same side was done at another hospital. Two years later a herniorrhaphy

and orchiopexy on the left side were performed. At the time of examination the patient was 22 years of age. He was a normal man. Both testicles were of good size and in the scrotum. However, repeated examinations of the semen failed to disclose spermatozoa. These 2 cases illustrate, as will several more, that the cosmetic result cannot be used as an index of fertility. The third patient was first seen in the clinic at 9 years of age, at which time both testicles were normal in size but were situated in the inguinal canal. At 13 years of age a Torek operation was performed on the right testicle, and the left was allowed to remain in the canal in the belief that it would soon descend. The patient was 20 years of age on examination. The left testicle, which was in the canal at the time of the first examination, remained there but was smaller than normal and was less sensitive. The right testicle was well in the scrotum, and remained attached to the lateral wall. This testicle was slightly smaller than normal, but was actively sensitive. The patient was unmarried. Examination of the ejaculatory fluid revealed only 6 or 7 spermatozoa per high power field in an undiluted specimen, too few for counting with the dilution method described previously. If one is to believe that 25,000,000 or more spermatozoa per cubic centimeter are usually killed by the vaginal secretions, this person must be considered essentially sterile. It is, however, still within the bounds of possibility that with artificial impregnation or proper regulation of intercourse he might foster his own progeny. For the purpose of clarity I shall classify this patient as potentially fertile to distinguish him from those of absolute fertility with an adequate sperm count or those of absolute sterility with no sperm.

The remaining 15 patients with bilateral undescended testicles were operated on at the Children's Hospital. With the exception of 2, one 3 years of age and one 5, all were operated on between the ages of 7 and 11. In all these the testicles either were located in the inguinal canal or were intra-abdominal, and in all there was some degree of herniation. Freeing of the cord and, when necessary, retroperitoneal dissection without fixation of the testicle in the scrotum constituted the method of orchiopexy used. On only one occasion were the vessels of the cord cut. In this instance complete atrophy of that testicle had taken place. On discharge from the hospital at the end of seven or eight days after operation both testicles were in the scrotum in all cases but 1. In this 1 case no testicle could be found on one side. A recent examination revealed that in 10 of the 15 patients both testicles were still well down in the scrotum. Of the remaining 5, 1 patient had only one testicle originally. In 3 there was one testicle, normal in size, well in the scrotum, with the other retracted into the inguinal canal and atrophied to from one-half to one-third the normal size. In the fifth patient both testicles had retracted into the inguinal canal and were markedly atrophied. In addition, this patient had contracted a marked gonococcic infection which finally cleared under prolonged treatment. The combination of these two factors rendered the patient totally sterile. There was no venereal disease in any of the rest of this group.

Of these 15 patients 6 have been married and have had one or more children. Counts of the spermatozoa could not be obtained on all of these persons so as to determine whether they were really the fathers of these children. However, a careful sexual history has led me to believe that they were, although in some, definite microscopic evidence of actively motile spermatozoa is still lacking. In 5 more, as yet unmarried, the counts were 92,000,000, 38,000,000, 50,000,000, 84,000,000 and 38,000,000. This indicates that 11 of 15 patients were definitely fertile. The cases of the remaining 4 need more careful consideration. The first patient was the one mentioned previously in whom both testicles had retracted and atrophied. There were no spermatozoa in the ejaculatory fluid. The second

patient had a routine orchiopexy performed when 11 years of age. When he was 22 examination revealed the right testicle to be normal in size but located in the inguinal canal while the left was normal in size and in the scrotum. Examination of the spermatic fluid on only one occasion revealed no spermatozoa. Repeated attempts to have this person return for a second test have met with no success. I think it is perhaps unfair to classify this patient in the sterile group on the basis of one examination, but until spermatozoa are proved to be present this must stand. The third patient had a routine orchiopexy at the age of 11. He was 22 years of age on examination. Both testes were of normal size and sensation and were well down in the scrotum. Examination of the ejaculatory fluid revealed 4,000,000 sperm per cubic centimeter. The fourth person had a routine orchiopexy at the age of 7. On examination he was 24 years of age. Both testicles were in the scrotum; the left was normal in size and sensation, and the right was slightly smaller and less sensitive. Counts of the spermatozoa repeatedly showed only from 5 to 7 normal spermatozoa per cubic centimeter. The last two patients must be considered essentially sterile on the basis that there were too few spermatozoa. However, even though it seems unlikely on the basis of all scientific data, they probably should be classified as being potentially fertile as long as there is even 1 active spermatozoon in an entire ejaculation.

In summary, among the patients with bilateral nondescent of the testicles there were 3 with no spermatozoa on repeated examination, 1 with none on one examination, 3 potentially fertile with active spermatozoa, but not in adequate number for normal fertility and 13 definitely fertile. Two of the 13 were not operated on; thus there were 11 operative cases of proved fertility. All of the 11 patients were operated on at the Children's Hospital.

The group of patients with unilateral undescended testicle on which studies of fertility have been carried out numbers 69. Seven of these were seen at the Children's Hospital between the ages of 2 and 7. At that time one of the testicles was either in the inguinal canal or in the abdomen. These 7 patients never had an operation performed and returned for examination at ages varying from 20 to 36 years. On examination, in every instance the testicle was found still to be in the inguinal canal and markedly atrophied. Counts of spermatozoa were not done on the married patients, of whom there were 3, as each had had a child. Counts carried out on the 4 unmarried patients were 30,000,000, 50,000,000, 74,000,000 and 130,000,000 per cubic centimeter.

Nine more patients of the 69 seen at the Children's Hospital during childhood were operated on elsewhere. In all instances the undescended testicle could be palpated in the canal on the initial examination. Exact description of the type of operation performed was lacking in some instances. In 3 cases it was known that orchidectomy was done, and in another the vessels were cut. In each, the operation was performed between the ages of 17 and 24. Recent examination revealed the testicle to be absent in the 3 cases in which orchidectomy was done, completely atrophied in 3 more and of good tone and in the scrotum in 3. Four of the patients had children. For 2 of these 4 I have no count, but for the other 2 the counts were 16,000,000 and 26,000,000 per cubic centimeter, respectively. This is interesting in view of the fact that a man with a count of 16,000,000 per cubic centimeter, less than the supposedly required number of spermatozoa, has had three normal children. The counts in the others were 40,000,000, 42,000,000, 49,000,000, 68,000,000 and 104,000,000.

The remaining 53 patients in this series with unilateral undescended testicles were operated on at the Children's Hospital. Nine of them were operated on under 5 years of age and the remainder between 5 and 11. Each patient had an

accompanying hernia. Routine orchiopexy, with retroperitoneal dissection when necessary, was performed on 48 patients. Of the remaining 5, the vessels were cut in 4, and in 1 the testicle was fixed into the scrotum and to the thigh by a silkworm stitch which was removed at the end of ten days. In all 5 there was marked atrophy of the testicle. In the other 48, on whom routine orchiopexy was performed without fixation, the testicle was in the scrotum in 35 and had retracted back into the canal in 13. Of the 13 in whom retraction had occurred, partial atrophy was present in 4 and complete atrophy in 9. Of the 35 in whom the testicle remained down in the scrotum, partial atrophy was present in 17, complete atrophy in none and a normal testicle in 18. To sum this up from a cosmetic standpoint, we can say that in those cases in which the vessels were cut or the testicle was fixed in the scrotum the result was poor. Approximately 30 per cent of the patients having routine orchiopexy had a poor result in that the testicle retracted and atrophied completely or in part. In the remaining 70 per cent the testicle was well in the scrotum.

The relative fertility of these patients is much harder to evaluate since one testicle was originally normal in size and position. It was thought impossible to catheterize the ducts and to collect separate specimens from each testicle during ejaculation. The count of spermatozoa thus becomes less valuable as an index of absolute fertility in this group. It is of paramount interest to discover not whether these persons are fertile but whether they are normally fertile when the testicles appear to be normal (i. e., to be well descended and equal in size). It is also of interest to know if the fertility is measurably diminished in persons in whom there is complete atrophy of one of the testicles. Of this group of 69 patients with unilateral undescended testicle, 21 have had children. Counts of spermatozoa were done on 54, and in only 3 instances were there less than 25,000,000 per cubic centimeter. One patient had had a repeated gonococcic infection which was arrested at the time of the test. Repeated specimens showed no spermatozoa. Examination of the testicles revealed the left to be normal and the right, which had originally been undescended, now in the scrotum, but only one-half the size of the left. In the second case the testicles appeared to be normal in size and position. Cosmetically the result was excellent. Repeated counts over a period of eighteen months showed only from 6 to 10 sperm per high power field in an undiluted specimen. In the third case only one test was done. At that time there were only 2,000,000 sperm per cubic centimeter in the specimen and yet this patient had three normal children. He was 44 years old, and all three children had been born during his early thirties. For the four years preceding examination no contraceptives had been used, yet the man married for a second time and wished to have children by the new union. It is entirely possible that fertility has reached a definite period of decline and that further progeny might be impossible. Further studies will be carried out in this case at definite intervals to see if there is any further measureable decrease.

Except for these 3 patients whose counts were low the remaining 51 showed counts varying from 25,000,000 to 175,000,000 per cubic centimeter. In only 3 was the count over 100,000,000. In these 3 the testicles appeared to be normal, and in 1 there seemed to be three testicles. In the patients in whom there appeared to be excellent results the counts ranged the entire scale. The counts for the patients in whom one testicle was atrophied also varied from low to high. Consequently one is led to infer one of two things: either that atrophy of one testicle does not materially affect the fertility of that individual or that the count of spermatozoa is not an accurate enough factor with which to measure relative fertility. I must tend to the latter view, because I believe the method used in

testing these patients is subject to too many mechanical errors in collection, dilution and count. The future study of relative fertility will then have to depend on a more accurate method of counting. However, the present tests on the patients with unilateral cryptorchidism have been uniform in consistently showing that except for 3 high counts, all of the specimens collected were below normal, 50 per cent of the counts being below 50,000,000 per cubic centimeter.

SUMMARY

A résumé of the fertility of persons with normally descended testicles has been made so that it will serve as a standard on which to compare the data for the persons with undescended testicles. The methods of orchiopexy have been reviewed. The studies of fertility of 89 men with undescended testicles have been compiled in an attempt to determine their fertility or relative fertility. Because the series is too small and the mechanical index too variable for evaluation of relative fertility one can draw only three definite conclusions:

1. Except in a small percentage of cases the fertility of all persons with cryptorchidism seems to be lower than that of the normal person. The same type of investigation and method of counting has been used in both groups.

2. The cosmetic result after orchiopexy cannot be used as a criterion of fertility.

3. In 18 patients with bilateral undescended testicles on whom orchiopexy had been done, there was definite fertility in 11, and in 3 more, in whom the counts were lowered but active sperm were present, potential fertility. The percentage of definite fertility in persons who have undergone orchiopexy may then be computed as 61 per cent in contrast to the estimated 10 per cent in persons without orchiopexy. If one is to add the 3 cases in the group with potential fertility, the percentage is raised to 77. In my opinion these statistics definitely make orchiopexy a justifiable procedure.

My main purpose in this paper has been to stimulate an interest in other clinics to carry out a similar type of investigation. I hope this will be fulfilled. I intend to continue the investigation and at a later time will report on a larger series in which something more definite can be offered in correlation of the types of orchiopexy with the resulting spermatogenesis.

NOTE.—Since this paper was submitted for publication more patients with bilateral undescended testicles have been found and examined and counts of their spermatozoa have been made. All 4 were seen and operated on at the clinic of the Children's Hospital between 4 and 9 years of age. At the initial examination in each case both testicles were found in the inguinal canals with an accompanying herniation. At recent examination their ages varied from 21 to 26 years. In all

instances both testicles were well in the scrotum and normal in size, shape and sensation. None of the men are married or have had children, but the counts on their ejaculatory fluid were 30,000,000, 30,000,000, 46,000,000 and 60,000,000.

If this group is added to others reported in the article the total percentage for proved fertility in these abnormal cases is raised from 77 to 82 per cent.

CYSTIC HYGROMA OF THE NECK

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Cystic hygroma of the neck is a comparatively rare condition and generally appears in children under the age of 5. It does, however, occur in adults, and my report includes the case of a patient 37 and another of a patient 18. Dr. Charles N. Hyatt reported two cases in which this condition occurred in adults, one patient being 19 and the other 20 years of age. It is usually present at birth or occurs sufficiently soon after birth to indicate that the condition is probably a developmental error. Arnold,[1] who studied this condition most thoroughly as far back as 1865, concluded that a congenital defect was the underlying cause. Thompson and Keiller,[2] in 1923, almost conclusively proved the following theory of origin to be true: In the 6 week embryo, the development of the lymphatic system is begun with the formation of the so-called lymph sacs, four in number, two being located between the carotid and the subclavian artery, one on either side, and two in relation to the iliac arteries. The main outgrowths of the first two mentioned form the lymph channels of the head, the neck and the arm; those of the other two, the lymph channels of the lower extremities and of the pelvis. The primitive lymph sacs later atrophy. Independent of this system, small islands of lymphoblastic cells are formed which develop into lymph vessels, later joining the larger system. This development probably takes place not only throughout intra-uterine life but during the subsequent first two years of the child's life. It is feasible to conclude from this description that hygroma may originate in the persistence of the primary lymph sac, in an offshoot of the sac or as a result of an island's detaching itself from the rest of the lymphatic system. Its final development may occur a few years after birth because its ancestral lymphoblasts were of the slower developing variety. It is possible for hygroma to develop in any region where the original lymphoblastic material is laid down. Clinically, it occurs most commonly in the cervical and axillary regions, rarely in the groin and almost never elsewhere. When hygroma involves deep structures of the neck or

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1. Arnold, Julius: Zwei Fälle von Hygroma colli cysticum congenitum, Virchows Arch. f. path. Anat. **33**:209, 1865.

2. Thompson, James E., and Keiller, V. H.: Lymphangioma of the Neck, Ann. Surg. **77**:385 (April) 1923.

of the axilla, it is because lymphatic tissue was previously laid down in that region and the cysts pushed their way out, rather than because the peripheral cysts dissected their way in. A cyst follows the path of least resistance, which is to the surface. To date, no specific cause has been found for the existence of hygroma; it is undoubtedly a lymphangiectasis. The most satisfactory explanation of the existence of cystic hygromas is that embryonic sequestrations of lymphatic tissue existed and that they had the power of persistent irregular growth.

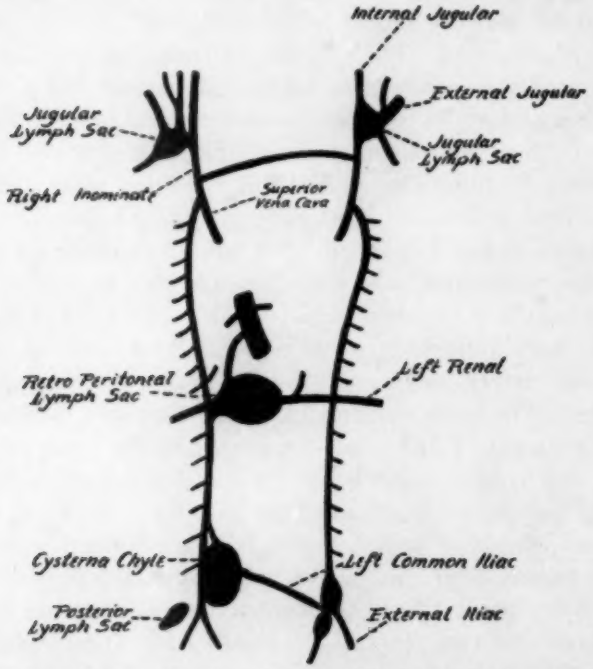

Fig. 1.—Schematic drawing showing the principal lymph sacs in their relation to the vascular system.

The term cystic hygroma of the neck should be restricted to thin-walled cysts lined with endothelium containing a serous fluid and having a marked power of growth. The cyst may be single or multilocular, and it may attain very large size. The endothelium is made up of a single layer of cells having the appearance of a mosaic. Any rapid increase in the size of the tumor is due to an increase in the lymph content, since no evidence of increased cell division has been shown nor does other evidence of malignant tissue exist. Hygroma of the neck usually is situated immediately lateral to the carotid sheath and anterior to the cervical nerve roots. It often extends down under the clavicle for a short distance, lying on the pleura. In his comprehensive report

of all cases on record to 1913, which totaled ninety-one, Dowd [3] described one case in which the growth practically covered the upper part of the left side of the chest anteriorly. At operation, the cysts lay beneath the pectoralis major muscle, almost completely enveloping the pectoralis minor muscle and extending under the clavicle of the neck beneath the subclavian vessels. In the cases reported by Dowd, forty patients were definitely cured, the treatment for most of them being total operative excision, and thirty-nine died. Hyatt [4] was not able to find more than sixteen cases of hygroma of the neck reported over the period from the time of Dowd's report in 1913 to 1932. In Hyatt's review of cases, two patients, one 19 years of age and the other 20, had cystic hygroma of the neck of from six to twelve months' duration.

In seventeen cases of cystic hygroma of the neck from the New York Post-Graduate Medical School and Hospital, the variation of age was rather marked. In this series of patients, the condition predominated in men. The history of sudden increase in size of the cyst lasting for two or three days, followed by sudden decrease, was noted. In several instances the cyst was aspirated by a physician outside the hospital, undoubtedly for the purpose of diagnosis since it assuredly could not have been for radical cure.

In case 6 of the series that I am reporting, a serious swelling followed an aspiration performed at another hospital. Consequently, the patient was admitted to the New York Post-Graduate Medical School and Hospital in a critical condition. The cyst was of the multilocular variety and was extensive.

REPORT OF CASES

The last operation performed on a patient with this condition in the New York Post-Graduate Medical School and Hospital took place on Nov. 3, 1934. Dr. Charles G. Heyd performed the operation. A detailed report of the case follows:

CASE 1.—S. L., a girl 16 months old, was admitted to the hospital on Oct. 20, 1934. She had a tumorous growth about two-thirds the size of an orange on the right side of her neck over the right clavicle between the ramus of the mandible and the clavicle, as shown in figure 2. The overlying skin was movable and not inflamed. The mass could be punctuated but was not tender. It was of two months' duration and had appeared first as a small lump which gradually had increased to its present size.

Physical examination showed the child to be normal in every respect, and the family history was not contributory. The child had never had a contagious or

3. Dowd, Charles N.: Hygroma Cysticum Colli: Its Structure and Etiology, Ann. Surg. **58**:112 (July) 1913.

4. Hyatt, Charles N.: Hygroma Cysticum Colli: A Case Report with a Review of the Literature, J. Iowa M. Soc. **22**:406 (Aug.) 1932.

infectious disease prior to the examination. About two weeks previous to the date of admittance the patient had been examined by another physician, outside the hospital, who had aspirated about 15 cc. of a dark red fluid from the tumorous mass.

Laboratory tests of the blood and of the urine showed both to be normal, except for the presence of many bacteria and a few squamous epithelial cells in the urine.

The preliminary diagnosis was a multilocular cyst or a cystic hygroma of the neck.

Roentgen examination showed a large, soft tumor in the right cervical area, of smooth contour and of homogeneous consistency and apparently without definite osseous connection. It resulted in a slight elevation and deviation of the laryngeal shadow. No gross pathologic change in either pulmonary field was observed. The conclusion was that a large, soft tumor existed in the right cervical area.

On November 3, Dr. Charles G. Heyd excised the tumor by operation. The operation was entirely uneventful and proved successful.

Fig. 2.—Showing cystic hygroma on the right side of the neck. The mass contained clear fluid and was lined with endothelium.

The patient had an uneventful recovery from the operation. She rested, slept and ate well. A slight serous discharge was noted on the dressing for the first two days following the operation. The child was rather listless until the morning of November 6, when there was a profuse purulent drainage, after which she seemed to be brighter and started to use her right arm without apparent difficulty. A comfortable convalescence continued until her discharge from the hospital on November 12. The patient returned to the hospital later for examination and was found to be in excellent health, the wound having healed nicely.

Pathologic Report.—The specimen measured in its collapsed state 60 by 50 by 30 mm. It consisted chiefly of an incised cyst the contents of which had been evacuated. The wall of the cyst was of fibrous tissue from 2 to 3 mm. in thickness. Its inner surface was smooth and pale gray except for fine white or reddish streaks. One portion of the wall of the cyst was thickened by fibrous tissue and fat which were adherent to the outer surface. On section, this portion of the wall contained cystic areas filled with coagulated opaque jelly suggesting mucus. Between these cystic spaces, there was fat, and covering the surface in this area there were tabs of muscle.

Microscopic Examination.—Sections through the walls of the various cysts presented the same picture. The cysts were lined by one or two layers of flattened cells, which in a few areas were cuboidal with pink-staining cytoplasm. The underlying stroma was formed in part of fairly young fibroblasts running in various directions and in part of myxomatous tissues. About scattered capillaries there was lymphocytic infiltration, fairly abundant in some areas. In the deeper layers of the wall, there were blood vessels with sclerosed walls and cross-sections of fairly large nerve trunks. The proliferation of fibrous tissue extended in delicate strands into the surrounding fat, where occasional capillaries were surrounded by lymphocytes. In some areas, the lymphocytic infiltration was marked throughout the wall. The content of the cyst was a mixture of mucus and albumin, and only one or two mitotic figures were seen in the entire section examined.

Diagnosis.—The condition was diagnosed as a multilocular cyst with associated chronic inflammation, especially fibrosis.

The following review includes some of the most interesting cases of this condition in patients treated in the New York Post-Graduate Medical School and Hospital.

CASE 2.—M. S., 14 years of age, noticed a swelling which appeared on the right side of the neck two years before consultation. It remained stationary for six months and then suddenly became markedly increased in size.

The pathologic report, dictated by Dr. Paul Klemperer, recorded the measurements of the specimen as 120 by 20 mm. The histologic picture showed a few large cavities which were empty and lined throughout with endothelium.

The next case represents an instance of the early occurrence of the condition.

CASE 3.—C. M., 1 month old, was admitted to the hospital on Aug. 31, 1922. There was a swelling on the right side of the neck which had been present since birth. It had grown larger continually. As illustrated by figure 3, it occupied the entire space between the mandible and the right clavicle. The cyst had grown into and penetrated the sternocleidomastoid, the digastric and the mylohyoid muscle. It was excised in toto from the submaxillary region, but there was a prolongation along the carotid vessels which extended posteriorly into the muscles in the back of the neck that made it impossible to dissect out the cyst cleanly. The cavity was treated with phenol successfully.

This case was particularly interesting because it showed how these cysts or their prolongations can penetrate or push through other structures. It also demonstrated the impossibility of a clean dissection, especially in the multilocular variety of cystic hygroma of the neck when it has invaded the mediastinum.

CASE 4.—A boy, aged 1½ years, was brought to the hospital by his mother, who first noticed a swelling on the right side of his neck when he was 3 weeks old. It had been growing larger almost constantly. Operation revealed a multilocular cyst extending up to the internal jugular vein, which made operative removal very difficult. It was totally excised.

Case 5.—J. L., a boy 4½ years old, presented a tumor on the right side of the neck. The swelling was first noticed two and a half years before consultation and had gradually increased in size.

The collapsed cyst measured 3 cm. in length and 1.5 cm. in diameter and was lined with endothelium.

Case 6.—L. G. was a girl aged 4 years and 3 months. About three and a half months previous to the patient's admittance to the hospital the mother noticed a small lump on the right side of the child's neck. For a period of three or four weeks, it remained the same size. It then began to enlarge and steadily grew in size until the operation, which was performed at another hospital on Oct. 5, 1927. Following the operation, the tumor grew much more rapidly than before. Two weeks after the operation, it was aspirated and a bloody serum was obtained. The child was admitted to the New York Post-Graduate Medical School and Hospital on Nov. 24, 1927. The tumor was completely excised, and the wound healed nicely.

Fig. 3.—Showing cystic hygroma of the neck and of the chest.

The fibromembranous mass measured 7.5 by 4 by 1.3 cm. and contained numerous opened cavities which appeared to communicate with each other. The cavities were lined with endothelium.

Case 7.—I. H., a girl 18 years old, for a year previous to her admittance to the hospital had noticed a small lump on the right side of her neck which had increased gradually to the size of a hen's egg. For a period of two or three days, it would increase very much in size and then would decrease slowly to its original size. An operative excision was performed and two pieces of membrane, the one 45 by 25 mm. and the other 40 by 8 by 8 mm., were removed.

Case 8.—F. L., a man 36 years old, for three years previous to his examination at the hospital had noticed a swelling on the right side of his neck which gradually had increased in size. It was about 2 inches (5 cm.) in diameter and, at times, greatly increased in size. The tumor was removed by operative excision. It was a thin-walled cyst and measured 32 mm. in diameter and less than 1 mm. in thickness.

I have reviewed in this series not only a few cases which illustrate the usual characteristics of this condition but some which presented unusual surgical complications. Since the tumor arises in a region of the body which is interspaced with a complicated maze of important blood vessels, nerves and muscles, it is of paramount importance that the physician, before attempting to treat this complication, thoroughly acquaint himself with the nature of the various phases of the condition and the region in which it occurs.

CONCLUSIONS

The unfamiliarity of the medical profession in general with the condition known as cystic hygroma of the neck is rather surprising, to say the least. Its importance to the surgical clinician is apparent since it must be considered when a differential diagnosis of the surgical conditions of the neck is being made. The prognosis must be very guarded in the cases of the multilocular variety. Thorough removal is the ideal procedure in the case of a unilocular cyst or in the case of the multilocular variety, when it is not very extensive.

Radical operative procedure is not to be considered when roentgenograms reveal that the multilocular cyst extends across the neck and down to the mediastinum, especially when the cyst has been aspirated and a 15 per cent solution of an iodized poppy-seed oil which has been diluted with poppy-seed oil is injected. For this condition, there is the choice of two treatments: (1) repeated aspirations, which must be performed under strict aseptic conditions to avoid contamination which might prove fatal and followed by the injection of a sclerosing fluid such as sodium morrhuate, which was used by Harrower [5] in the successful treatment of this condition in one of his cases; (2) roentgen therapy after first reducing the size of the cyst by aspiration, as recommended by Figi.[6]

Early diagnosis and radical operation when the cyst is small would avoid serious complications later.

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5. Harrower, Gordon: Treatment of Cystic Hygroma of the Neck by Sodium Morrhuate, Brit. M. J. **2**:148 (July 22) 1933.

6. Figi, Frederick A.: Radium in the Treatment of Multilocular Lymph Cysts of the Neck in Children, Am. J. Roentgenol. **21**:473 (May) 1929.

BACTERICIDAL EFFECT OF HIRUDIN AND HEPARIN

I. INTRAVENOUS INJECTION OF HIRUDIN AND OF HEPARIN AND LEECHING IN EXPERIMENTAL BACTEREMIA

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AND

HOWARD R. MAHORNER, M.D.

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Interest in leeches has been revived by the reports of excellent results obtained from their use in the treatment of phlebitis by Termier,[1] Sulger and Bozsin,[2] Mahorner and Ochsner[3] and others. Attention given to the active substance, hirudin, secreted by these annelids is opportune, since the reports on the results of this method of treating phlebitis continue to confirm its value and injections of hirudin offer a possible substitute for the application of leeches, which evoke a feeling of revulsion in the patient.

In a previous paper we discussed the action of hirudin and called attention to the report by Bosc and Delezenne[4] on experiments undertaken to determine whether hirudin exerted any bactericidal effect on micro-organisms. They found that hirudinized blood produced precipitation of Bacillus coli in vitro more effectively than the same amount of blood not hirudinized. In vivo experiments were undertaken by the same authors. After injections of sufficient hirudin to render the total volume of blood incoagulable, at subsequent intervals of from fifteen to forty-five minutes they injected into the blood stream of the animals lethal doses of colon bacilli or streptococci. The control animals died promptly, but the hirudinized animals recovered.

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1. Termier, J.: Grenoble-Abortive Treatment of Surgical Phlebitis with Early Leaving of Bed, Procés-verbaux et mém., Cong. de chir. **31**:49, 1922; Grenoble-Abortive Treatment of Surgical and Obstetrical Phlebitis Through Hirudinization (Application of Leeches), Compt. rend. Cong. de chir., Paris, 1925, p. 434.

2. Sulger, E., and Boszin, T.: Ueber die post-operative Thrombose und Embolie sowie ihre therapeutische und prophylaktische Behandlung mit Blutegeln, Deutsche Ztschr. f. Chir. **216**:175, 1929.

3. Mahorner, H. R., and Ochsner, A.: The Use of Leeches in the Treatment of Phlebitis and the Prevention of Pulmonary Embolism, Ann. Surg. **98**:408, 1933.

4. Bosc and Delezenne: Imputrescibilité du sang rendu incoagulable par l'extrait de sangsue, Compt. rend. Acad. d. sc. **123**:465, 1896; De l'immunité conférée par quelques substances anticoagulantes. De son méchanisme: excitation de la phagocytose, augmentation du pouvoir bactéricide du sang, ibid. **123**:500, 1896.

We became interested in this subject because of our clinical observations concerning the use of leeches in the treatment of phlebitis. The report of Bosc and Delezenne [4] stimulated us to investigate the possibility of a protective action of hirudin against bacteremia.

Because, as we discussed in our former article, the beneficial effects in the treatment of phlebitis with leeches may be attributed possibly to the softening of the clot by an anticoagulant and possibly to the antagonistic action on the inflammation, we used in the present investigation another anticoagulant, heparin, partly as a control and partly as a possible substitute for hirudin in the treatment of phlebitis. Hirudin at $150 a gram was almost prohibitive for clinical use or experimentation on a large scale. Heparin differs from hirudin in its action on blood in the following particulars: It is obtained from liver and is found in small quantities in the circulating blood. According to Howell,[5] it reacts with prothrombin so as to prevent its activation into thrombin. However, heparin as well as hirudin is nontoxic to the animal organism in quantities sufficient to prevent coagulation of the drawn blood. Shionoya [6] stated that I mg. of heparin renders 100 cc. of human blood incoagulable for twenty-four hours or more, and that from 20 to 25 mg. of heparin per kilogram of body weight administered to animals prolongs the clotting time to from thirty minutes to several hours. Though it is not known exactly how hirudin acts, it is thought by Howell [5] to react with thrombin so as to prevent the latter's action on fibrinogen. Barratt [7] shared this view of the anticoagulant effect of hirudin, but Bodong [8] thought that hirudin acted as an antifibrinogen, and Gratia [9] believed it to be an antithrombin and Arthus,[10] an antiprothrombin. However, not one of these theories completely explains the action of hirudin on blood. When a few cubic centimeters of blood is allowed to clot in a test tube and a few milligrams of hirudin is sprinkled in, the blood becomes fluid again.

For our in vivo experiments we used forty-one dogs. There were fifteen controls in which bacteremia was induced by the method described

5. Howell, W. H.: The Purification of Heparin and Its Presence in the Blood, Am. J. Physiol. **71**:553, 1925.

6. Shionoya, T.: Studies on Experimental Partial Thrombosis; Effects of Certain Anticoagulants (Heparin and Hirudin) on Extracorporeal Thrombosis and on Mechanism of Thrombus Formation, J. Exper. Med. **46**:19, 1927.

7. Barratt, J. O. W.: Anticoagulant Action of Hirudin, Brit. J. Exper. Path. **7**:127, 1926; Action of Hirudin upon Thrombin, J. Physiol. **64**:47, 1927.

8. Bodong, A.: Ueber Hirudin, Arch. f. exper. Path. u. Pharmakol. **52**:242, 1904-1905.

9. Gratia: Méchanisme de l'action anticoagulante de l'hirudine. La neutralisation réciproque de l'hirudine et de la thrombine, Compt. rend. Soc. de biol. **83**:311, 1920.

10. Arthus, quoted by Barratt.[7]

herewith. No hirudin or heparin was given. In eleven dogs bacteremia was induced, and intravenous injection of heparin was given. In eight dogs bacteremia was induced, and leeches were applied to the skin. In one dog bacteremia was induced, and hirudin was injected intravenously. In three dogs used as controls hirudin was injected intravenously, and in three more dogs used as controls leeches were applied to the skin.

METHODS

Production of Bacteremia.—The suspension of bacteria injected intravenously into the dogs to induce bacteremia was obtained in the following manner: The forty-eight hour growth on meat infusion agar plates (Petri dishes) inoculated with staphylococci was suspended in physiologic solution of sodium chloride in the proportion of twelve plate cultures to approximately 3 ounces (60 cc.) of solution of sodium chloride. This suspension was injected intravenously into the dogs, each animal receiving 0.5, 1, 2, 4 or 8 cc. per kilogram of body weight. With this dose it was hoped that among controls receiving injections of the suspension alone the dogs receiving the larger doses would die and those receiving smaller doses would live. Temperatures were recorded before inoculation and at subsequent periods of from one hour to three days. They were observed after that, but no records of temperature were made after the first three days.

Treatment of Bacteremia with Leeches or Hirudin.—Five leeches were applied to each of eight dogs into which the suspension of staphylococci had been injected intravenously. Two of the dogs received 0.5 cc. of the bacterial suspension per kilogram of body weight; two, 1 cc.; two, 2 cc.; one, 4 cc., and one, 8 cc. In addition, one dog receiving 4 cc. of the culture per kilogram of body weight was given 21 mg. of hirudin intravenously. About 7 mg. of hirudin may be extracted from one leech. It is assuming too much, however, to consider that when a leech is applied and sucks its fill it delivers its entire hirudin content into the systemic circulation.

Treatment of Bacteremia with Heparin.—Heparin in solution, a dose of 30 mg. per kilogram of body weight, was injected intravenously into eleven dogs in which bacteremia was induced at the same time by an intravenous injection of the suspension of staphylococci. Two of these dogs received doses of 0.5 cc. of the suspension per kilogram of body weight; two, 1 cc.; two, 2 cc.; two, 4 cc., and three, 8 cc. Each of the dogs had a control which received an identical dose of the staphylococcus suspension but no heparin.

Treatment of Controls with Heparin and Leeches.—Thirty milligrams of heparin per kilogram of body weight was injected intravenously into each of three dogs, and five leeches were applied to the skin of the abdominal wall of each of three other dogs. These six dogs were used as controls.

RESULTS

The results are stated briefly in the table.

Controls.—The three dogs to which heparin alone was given and the three dogs to which leeches alone were applied all lived and showed no untoward effects. As we had hoped, the dose of staphylococcus suspension was so selected that those dogs receiving a minimum dose usually lived while those receiving the severe and moderate doses died.

Thus, of the fifteen dogs into which staphylococci alone were injected intravenously, four lived. The fifteen dogs were divided into three series. Thus three dogs received 0.5 cc., three, 1 cc., three, 2 cc., three, 4 cc., and three, 8 cc., of the suspension of bacteria per kilogram of body weight. The dogs that survived were the three that received

Results of Experiments on Dogs with Intravenous Injections of Hirudin and of Heparin and with Leeches

Dog	Dose of Staphylococcus Suspension, Cc. per Kg.	Number of Leeches	Dose of Hirudin, Mg. per Kg.	Dose of Heparin, Mg. per Kg.	Died	Lived	Group Results
1	0.5	..	..	..	Killed on 18th day		Mortality, 60%; average survival, 56 hours
2	1	..	..	..	Killed on 18th day		
3	2	..	..	..	49 hr.	..	
4	4	..	..	..	96 hr.	..	
5	8	..	..	..	24 hr.	..	
6	0.5	5	..	..	23 hr.	..	Mortality, 100%; average survival, 34 hours
7	1	5	..	..	122 hr.	..	
8	2	5	..	..	12 hr.	..	
9	4	5	..	..	12 hr.	..	
10	8	5	..	..	3 hr.	..	
			Second Group				
11	0.5	..	..	..	Killed on 8th day		Mortality, 80%; average survival, 27 hours
12	1	..	..	..	60 hr.	..	
13	2	..	..	..	36 hr.	..	
14	4	..	..	..	12 hr.	..	
15	8	..	..	..	1 hr.	..	
16	0.5	..	..	30	8 days (pneumonia)		Mortality, 80%; average survival, 60 hours
17	1	..	..	30	Killed on 8th day		
18	2	..	..	30	36 hr.	..	
19	4	..	..	30	12 hr.	..	
20	8	..	..	30	½ hr.	..	
21	..	5	..	..	.....	Lived	No mortality
22	..	5	..	..	.....	Lived	
23	..	5	..	..	.....	Lived	
24	..	..	..	30	.....	Lived	
25	..	..	..	30	.....	Lived	
26	..	..	..	30	.....	Lived	
			Third Group				
27	0.5	5	..	..	.....	Lived	Mortality, 50%; average survival, 29 hours
28	1	5	..	..	29 hr.	..	
29	2	5	..	..	29 hr.	..	
30	4	..	21	21	.....	Lived	
31	8	..	..	30	12 hr.	..	Mortality, 100%; average survival, 91 hours
32	0.5	..	..	30	5 days	..	
33	1	..	..	30	5 days	..	
34	2	..	..	30	6 days	..	
35	4	..	..	30	31 hr.	..	
36	8	..	..	30	5 days	..	
37	0.5	..	..	..	.....	Lived	Mortality, 80%; average survival, 49 hours
38	1	..	..	..	5 days	..	
39	2	..	..	..	29 hr.	..	
40	4	..	..	..	12 hr.	..	
41	8	..	..	..	36 hr.	..	

0.5 cc. of the suspension and one that received 1 cc. Since each of these dogs represented a control for a dog treated with heparin or with leeches or both, they will be considered in more detail with the series for which they were controls.

Treatment with Heparin.—In the first series of five dogs treated with heparin four (80 per cent) died, having an average length of life of

sixty hours, whereas of the five control dogs for this series four (80 per cent) died, having an average length of life of twenty-seven hours.

In the second series of dogs treated with heparin all six dogs died (100 per cent). The dog which survived longest lived six days, and the average duration of life of the series was ninety-one hours. Of the five controls for these six dogs (two of the six dogs treated with heparin received the same dose of the bacterial suspension) four died (80 per cent). The average duration of life of the four was forty-nine hours. All of the deaths occurred within five days.

The temperatures of the control animals showed very little difference from the temperatures of animals treated with heparin either when those of individual dogs treated with heparin were compared with those of their individual controls at different periods of time after injection or when averages were used of all the temperatures of an individual dog up to eighty-four hours or of the temperatures of all the dogs in the series at a definite period after injection. For all the dogs in the series except those which received large doses and died almost immediately there was a definite rise of temperature within two hours after injection to between 101 and 105 F. The fever gradually subsided after from twenty-four to forty-eight hours in the dogs that recovered.

Therefore, of the eleven dogs receiving heparin intravenously at the time bacteremia was induced only one lived, the mortality being 90.9 per cent. Two of these dogs had the same dose of the same culture and had only one control. There were thus only ten controls. Of these ten dogs two survived, the mortality being 80 per cent. The dog treated with heparin that survived was one that had received a small dose of the staphylococcus suspension, 1 cc. per kilogram of body weight. The control dogs that survived had received only a minimum dose of the suspension, 0.5 cc. per kilogram of body weight.

It might be concluded from these results that injections of heparin given intravenously do not protect an animal against a staphylococcic bacteremia.

Treatment with Leeches and Hirudin.—Of the first series of five dogs treated with leeches all died (mortality 100 per cent). The longest survival was one hundred and twenty-two hours, and the average length of time they survived was thirty-four hours. Three of the five control dogs in which bacteremia was induced died (60 per cent). All three deaths occurred within ninety-six hours, and the average length of time three dogs survived was fifty-six hours.

In the second series treated with leeches there were three dogs. One survived and two died (mortality 66.6 per cent). Both deaths occurred at the end of twenty-nine hours. Of the controls for these three dogs treated with leeches two died and one survived (mortality 66.6 per cent).

The average length of time the two dogs survived was seventy-four hours after receiving injections.

One dog received 21 mg. of hirudin intravenously at the same time that it received 4 cc. of the bacterial suspension per kilogram of body weight. This dog survived. Its control, receiving a similar dose of staphylococci but no hirudin, died in twelve hours. Moreover, it was the only dog receiving so large a dose of the bacterial suspension in the entire experiment that survived. From this fact alone no conclusion can be drawn.

Twenty-one milligrams of hirudin is the approximate amount which may be obtained from three leeches and is sufficient to render incoagulable only 150 cc. of blood. It is far less than the amount which must have been used by Bosc and Delezenne in their experiments, when they rendered the entire blood volume of their animals incoagulable. We are anxious to repeat this part of the experiment using hirudin intravenously in larger doses.

The temperature reaction in the dogs treated with leeches and in their controls was similar, but the average was a little higher in the control dogs than in those to which leeches had been applied.

It is obvious that leeches do not protect the animals from staphylococcic bacteremia, since of eight dogs treated with leeches seven died (87.5 per cent), whereas of the eight controls only 5 died (62.5 per cent). From our result it would appear that leeching increases the mortality. Doubtless a large, if not the entire, factor is the loss of blood. Each leech may suck approximately 15 cc., and some additional blood is lost from oozing. So each of the dogs treated with leeches lost a quantity of blood. This may explain in some measure the discrepancy of our results from application of leeches and intravenous injection of hirudin. The question is still unsettled from these experiments whether hirudin exerts a protective effect. Although this is possible and even suggested by the in vivo experiments, it would seem from the in vitro experiments that it has no such synergistic action on the responses of the defense mechanisms of the blood as was claimed by Bosc and Delezenne.[4]

Necropsy.—In those animals that died within a few hours after injection nothing was found at autopsy to account for the death, which must have occurred from an overwhelming toxemia.

In the animals that died in from twelve hours to two days small hemorrhages were found in the lungs, spleen and kidneys. In those animals dying after three days abscesses were found usually in the kidneys and sometimes in the lungs. In the subcutaneous tissue of the abdomen of some of the dogs to which leeches had been applied were found large ecchymoses.

SUMMARY

In order to determine the effect of leeches applied to the skin, of hirudin given intravenously and of heparin given intravenously on bacteremia, experiments were undertaken, forty-one dogs being used. Into thirty-five of the dogs a suspension of staphylococci was injected intravenously, each dog receiving one of five different doses, 0.5 cc., 1 cc., 2 cc., 4 cc. or 8 cc. per kilogram of body weight. Into three dogs used as controls heparin alone was injected intravenously, and to another three used as controls leeches alone were applied. Of eight dogs receiving leeches in addition to injections of the bacterial suspension intravenously seven died (87.5 per cent), whereas of their eight controls receiving analogous doses of the staphylococcus suspension but no treatment with leeches five died (67.5 per cent). Thus apparently leeching is an added factor in the production of death.

One dog received 21 mg. of hirudin intravenously in addition to a large dose of the bacterial suspension. This animal recovered and was the only one in the entire series receiving so large a dose of staphylococci that did recover. No conclusion is drawn. The discrepancy of the results obtained by leeching and by intravenous injection of hirudin may be due to the loss of blood by the former method.

Of eleven dogs receiving heparin intravenously in addition to the suspension of staphylococci ten died (90.9 per cent). Of their controls 80 per cent died. Thus heparin injected intravenously does not assist an animal in overcoming bacteremia and is apparently an added factor in increasing the mortality.

CONCLUSIONS

The application of leeches to dogs in which bacteremia has been induced increases the mortality. Hirudin injected intravenously may have some beneficial effect.

Heparin injected intravenously into dogs with staphylococcic bacteremia increases the mortality.

A REVIEW OF UROLOGIC SURGERY

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Anomalies.—Wiseman [1] expressed the opinion that before operation is undertaken for the relief of obstructive effects of a congenital anomalous formation of the urinary tract it is of the utmost importance to make a thorough and searching urologic study. According to Hunner, too many single kidneys have been removed on the assumption that the patient possessed a second kidney. It is important to determine beforehand the presence or absence, as well as the degree, of infection in the kidney which is to be subjected to a plastic procedure, the functional status of the involved organ and the possibility of bilateral involvement. A congenital urinary anomaly is a potential source of obstruction and of subsequent urinary stasis and infection. Anomalous blood vessels in close proximity to the upper third of the ureter, although not actually responsible for the collapse of the ureter, may, by their pulsations, interfere with the normal flow of the peristaltic wave down the ureter, and thereby promote stasis and pyelectasis. In the absence of demonstrable obstruction at the ureteropelvic juncture, or of the ureter, in a group of cases in which the condition was classified as being of idiopathic origin, Walters was able to demonstrate a subepithelial fibrosis at the pelvic outlet and occasionally faulty or lateral insertion of the ureter into the pelvis, which he regards as the contributing factor. The obstruction may be relieved by division of adhesions that

1. Wiseman, J. L.: Congenital Urinary Anomalies: An Evaluation of the Associated Obstructive Syndrome with Report of 6 Cases, Ann. Surg. **100**:445 (Sept.) 1934.

cause the angulation of an accessory ureter, or by division of an anomalous blood vessel. Unless the aberrant vessel is extremely small it should not be severed, because it is an end artery and its division really amounts to partial nephrectomy. It is possible to determine beforehand the vascular supply of the kidney which will be affected by division of an aberrant vessel, by temporary clamping with a rubber-covered hemostat. When the caliber of the vessel is too large to permit division without seriously affecting the blood supply of a large portion of the kidney, the ureter may have to be severed from the hydronephrotic sac and reimplanted at another point. Whenever there is a large redundant sac, resection will have to be performed in such a way that the ureteropelvic juncture at the conclusion of the operation occupies a position at the most dependent portion of the sac. The measure of success or failure of plastic and other conservative procedures for the correction of hydronephrosis and the contributory ureteral obstruction may be gaged by the alleviation of symptoms, by the pyelographic evidence of decreasing capacity of the sac, and by the return of its functional capacity as estimated by differential functional renal tests and, less accurately, by the density of the dye that is excreted following intravenous excretion urography.

Sangree, Morgan, Klein and Trasi [2] reported that symmetrical horseshoe kidney most commonly fuses by the lower pole, constituting the long kidney. It rarely fuses by the upper pole. Various degrees of dystopia and inclination to one side or the other may occur, represented by the "caked" kidney, the "sigmoid" kidney and the "L-shaped" kidney; these are classed as asymmetrical types. Fused kidneys are more commonly the seat of pathologic changes than are normal kidneys, especially those changes that are incident to urinary stasis. Before instituting surgical procedures for the treatment of horseshoe kidneys, the surgeon should consider the possibility of anomalous vessels, often multiple in number and variable in position. A wedge-shaped arrangement of calculi in a urogram should arouse suspicion of the presence of a fused kidney. Concomitant congenital anomalies should always be investigated in the study of a horseshoe kidney. In every case in which there is an abdominal mass and the triad of umbilical or lumbar pain, gastro-intestinal disorders and urinary disturbances, horseshoe kidney should be considered.

Stone.—Prather [3] said that nephrotomy is necessary at times in order to remove large branching calculi without sacrificing the kidney.

2. Sangree, Henry; Morgan, David; Klein, Thomas, and Trasi, Rocco: Horseshoe Kidney and the Relation of Nephritis and Calculous Formation to Anomalous Circulation: A Report of Twenty-Five Cases, J. Urol. **32**:648 (Dec.) 1934.

3. Prather, G. C.: A Method of Hemostasis During Nephrotomy for Large Kidney Calculi, J. Urol. **32**:578 (Dec.) 1934.

Operations which involve a large portion of the cortex of the kidney have rightfully been considered serious procedures, principally because of these four factors: (1) primary hemorrhage; (2) sepsis in the cortex of the kidney; (3) destruction of functioning tissue by the cortical incision or suture, and (4) secondary hemorrhage.

Pressure on the pedicle in one form or another for hemostasis during operation has been suggested by a number of operators. Manual compression between two fingers is objected to because the hand used in this manner may be in the way of the operator, and the fingers, acting as compressors, tire frequently and interrupt the surgeon. Temporary clamping of the pedicle is an effective method, which is easily applied, gives instantaneous control, and does not interfere with the operative field. However, care must be taken that the clamp shall not injure the walls of the vessels of the pedicle, and that the temporary anemia produced by clamping of the pedicle shall not be harmful to the kidney. Kümmel described a featherweight metal clamp for this use. Prather uses a semiflexible Doyen curved intestinal clamp, which is 9 inches (22.8 cm.) long, covered with soft rubber boots, and shaped so that in closing the clamp pressure is applied last in the middle of the blades. This clamp is applied to the pedicle after the ureter has been separated and retracted. The ureter is not included in the clamp. No damage to the vessels of the pedicle has been observed in cases in which such a clamp has been applied just tightly enough to produce hemostasis. The clamp has been released for from twenty to forty seconds at the end of eight minute to ten minute periods of compression, in order to allow the flow of blood through the kidney to be temporarily resumed.

In cases in which there are large branching calculi which form a cast of the kidney, with additional small stones, which sometimes occur in calices with narrowed infundibula, the accepted procedure, exclusive of nephrectomy, apparently has been a full length sagittal incision through Brödel's white line. This region has been falsely called an avascular area. In Prather's cases in which there were stones of the stag-horn type, he made a V-incision on the posterior surface of the kidney, with the apex of the incision at the pelvis, and with the ends of the incision extending toward each pole and over the stone. With a small retractor lifting the flap of cortex, the stone may be completely visualized and easily removed in one piece, without breaking off fragments. This incision is shorter than a full length sagittal one of the same kidney, and is made easily and quickly by placing the incision directly over the stone. By this method, more than half of the kidney is not touched by the incision or the sutures. After the stone has been removed, openings to all the calices are within sight, in a bloodless field, so that they may be explored easily if roentgenologic examination of the wound indicates remaining calculi. Hemostasis and adequate

exposure permit rapid, yet careful, removal of stones from a kidney. After roentgenologic examination has shown that there are not any remaining calculi, and a bougie has been passed down the ureter into the bladder to insure its patency, the nephrotomy incision is closed with 00 chromic catgut. A no. 18 F. Pezzer catheter is placed so that it emerges from the end of the incision at the lower pole. This should remain in place for from fourteen to sixteen days. The rapid rate of healing and postoperative pyelograms indicate that there is not any necrosis of the V-section of renal tissue.

Secondary hemorrhage can be diminished by placing the sutures close to the line of incision in order to avoid large infarcts and by always draining the kidney with an adequate nephrotomy tube. Irrigation through this tube is often advisable in order to keep the kidney free from clots.

With due regard for the futility of always doing extensive nephrotomy rather than nephrectomy, Prather expressed the opinion that at times it is inadvisable to remove the kidney. Nephrotomy is especially indicated in cases in which the patients are so-called "stone-formers," and in cases in which there are large stones in both kidneys. This procedure has made it possible to avoid nephrectomy without undue risk.

Prather reported a group of consecutive cases in which there had not been any secondary hemorrhage, and included reproductions of roentgenograms which were made before and after the operation.

Barney and Mintz [4] reported on a group of 18 patients who had hyperparathyroidism, which was proved by operation, 11 (61.1 per cent) of whom also had calculi in the urinary tract. These 11 patients are included among 104 with calculous disease previously reported on, giving a total of 10.5 per cent who had disease of the parathyroid gland. There are other patients in this group who may prove to have hyperparathyroidism, thus increasing this percentage considerably. These 11 patients who had urinary calculi, together with 7 others who did not have any calculi but who did have cystic degeneration of the bone, have all been operated on, the cases forming, in the opinion of the authors, a unique series. In most of the cases in which there was lithiasis, the parathyroidectomy followed the lithotomy.

Of the 18 patients, 12 (70 per cent) were females. The youngest patient was 13, and the oldest was 62 years of age, with an average age of 43 years. The value for the calcium varied from 11.5 to 16.8 mg. per hundred cubic centimeters of serum, with an average of 13.78 mg.; the value for the phosphorus averaged 2.55 mg. per hundred

4. Barney, J. D., and Mintz, E. R.: Some Newer Conceptions of Urinary Stone Formation, Tr. Am. A. Genito-Urin. Surgeons **27**:203, 1934.

cubic centimeters of serum and ranged from 1.4 to 4.7 mg. A value of more than 11 mg. per hundred cubic centimeters for the serum calcium and a value below 3.5 mg. for the serum phosphorus should always be an indication for investigation. Involvement of bones, ranging from large, multiple cysts to simple decalcification, was found in 12 cases (70.5 per cent). In 6 cases, urinary calculi and bony changes were found together. The stones were bilateral in 4 (36 per cent) of the 11 cases, and the urine was normal in 35 per cent of the cases. There was no operative mortality.

A careful reexamination of as many as possible of their patients who had urinary lithiasis and who were subjected to operation for removal of the stones has been instituted. To date 33 patients have been examined. The examination included quantitative estimation of the calcium and phosphorus in the serum and roentgenologic examination. Eleven (33⅓ per cent) of these 33 patients revealed the high value for the serum calcium which is so consistent with parathyroid disease.

Albright and Bloomberg [5] reported that hyperparathyroidism is so frequent a cause of the formation of stone in the urinary tract that it must be determined whether or not it is present in every case of this disease. Eleven cases are cited from a series of 23 proved cases of hyperparathyroidism at the Massachusetts General Hospital in which the presence of renal stones was the only indication that led to the diagnosis of the underlying disease. A frequent finding in cases of hyperparathyroidism is many finely granular casts in the urinary sediment. The granules have been shown to contain calcium, probably calcium phosphate. The casts can be made to change into hyaline casts as the urine is made more acid by the administration of ammonium chloride by mouth. Their continuous presence in large numbers is an indication that intrarenal damage is in progress. The factors governing the formation of these casts, which in a way are microscopic calculi in the renal tubules, are probably the same as those which govern the formation of stone in cases of hyperparathyroidism. These factors are the concentrations in the urine of calcium, phosphate and hydrogen ions. The formation of stone in cases of hyperparathyroidism belongs to that etiologic group in which the predisposing abnormal factor is an excess of crystalloids in the urine. This fact is justification for further attention to this line of approach in the solution of calculosis in general.

Keyser,[6] in discussing etiology of stone, said that he was successful in producing an excessive excretion of calcium oxalate in the urine of

5. Albright, F., and Bloomberg, Esther: Hyperparathyroidism and Renal Disease with a Note as to the Formation of Calcium Casts in This Disease, Tr. Am. A. Genito-Urin. Surgeons **27**:195, 1934.

6. Keyser, L. D., in discussion of Joly, J. S.: Etiology of Stone, J. Urol. **32**:575 (Dec.) 1934.

rabbits by simultaneous subcutaneous injections of butyl oxalate and calcium chloride. The first appearance of oxalate crystals in the urine revealed their morphology as that of isolated octahedrons. With intensification of the excretion, there appeared spherical crystals, which had a tendency to agglutinate, fuse and form stones. According to the laws of crystalline precipitation from colloidal solutions, Keyser demonstrated that the urinary colloids would carry a certain amount of oxalate in solution. A further saturation resulted in the deposition of isolated octahedral units, while an excretion of amounts beyond the power of the colloids to deposit isolated crystals resulted in colloidal inadequacy; as a consequence, there fell from solution crystals of spherical form in such profusion that they became agglutinated to form concrements. Previous work with calculi, which were produced by the feeding of oxamide, had suggested a similar mechanism of hyperexcretion calculosis. This appeared to involve also a certain amount of deposition of urinary pigment in the forming stone. It was shown that experimental production of stasis augmented the deposition of stones when carried out in conjunction with the production of such crystalline hyperexcretion.

In the reports of a high incidence of calcium phosphate calculi associated with hyperparathyroidism, Keyser observed a clinical confirmation of the existence of a hyperexcretory type of formation of stone. The excessive excretion of calcium phosphate and its deposition as stone in cases of hyperparathyroidism markedly parallel the excessive excretion of calcium oxalate observed in experimental animals. Various observers noted intense phosphaturia, deposition of salts in the uriniferous tubules and nephritis. Likewise, Keyser found in animals an identical type of nephritis with deposits of oxalate crystals in the renal tubules. In this connection is cited the belief that uratic calculi are the result of excessive excretion of uric acid, and that uric acid tubular infarcts, which have been noted in infants, may be associated with stone.

Higgins [7] stated that in the experimental production of stones in rats by employing diets that were deficient in vitamin A, three constant findings were observed: (1) infection, (2) persistent alkalinuria and (3) keratinization or metaplasia of the epithelium of the renal pelvis, ureter and bladder. He is convinced that the infection was not the sole factor in the production of the stones. The incidence of infection did not keep pace with that of formation of stones in the early stages of the experiments. If ammonium chloride is added to the diet, tending to acidify the urine, it is more difficult to produce calculi. The chemical factors involved in the experimental production of stones may now be satisfactorily explained to satisfy the requirements stressed by colloidal

7. Higgins, C. C., in discussion of Joly,[82] p. 236.

chemists, and it unquestionably is true that the high alkalinity of the urine and keratinization of the epithelium are the important factors. Higgins expressed the opinion that vitamin deficiency disease is not the cause of all calculi, as lithiasis also is found associated with metabolic disease. There are also cases in which calculi are associated with hyperparathyroidism. Experimentally, calculosis can be produced in the parenchyma of the kidney by injection of parathyroid extract, but it has not been possible to produce stones in the pelvis of the kidney or in the bladder. It is only by careful interpretation and analysis of all the experimental work and correlation with all clinical observations that it may finally be possible to find a single etiologic factor associated with all calculous disease.

Lower [8] reported that it has been definitely proved experimentally that stones can be produced by depriving animals, particularly rats, of vitamin A, and that by restoring this vitamin to the diet, many of these stones disappear, according to roentgenographic evidence.

In applying this knowledge clinically, a diet rich in vitamin A has been prescribed for patients who have been subjected to operation for stones in the ureter or kidney. A small series of patients who had renal calculi and who refused operation or who had bilateral lithiasis have been receiving a special diet which is rich in vitamin A and which produces an acid ash. In each of 2 instances, a small stone in the lower calyx of the kidney, too large to pass spontaneously, has disappeared within four months, according to roentgenographic examination. In 2 cases, multiple large bilateral renal calculi have decreased definitely in size within thirteen months. One of the patients did not pass sand or calculi in the urine until she had taken the special diet for three months; the urine is now continually filled with sediment and small stones. Another patient had a large stone which completely filled the left kidney. In the six months during which he has taken the diet that is rich in vitamin A and productive of an acid ash, 323 small calculi have been passed. Previously, the patient never had passed sand or a stone in the urine.

Barney [9] said that at the Massachusetts General Hospital 104 patients who have had stone have been examined for parathyroid disease by an estimation of the calcium and phosphorus in the serum. A value of more than 11 mg. per hundred cubic centimeters for the serum calcium and a value below 3.5 mg. per hundred cubic centimeters for the serum

8. Lower, W. E., in discussion of article by Joly, J. S.: Etiology of Stone, J. Urol. **32**:570 (Dec.) 1934.

9. Barney, J. D., in discussion of article by Joly, J. S.: Etiology of Stone, J. Urol. **32**:573 (Dec.) 1934.

phosphorus should always arouse suspicion. Eleven (10.5 per cent) of these patients were found to have hyperparathyroidism. These 11 patients, together with 7 others who had no stone but who had other manifestations of the disease, such as bone cysts and decalcification, were all operated on, and the parathyroid tumor removed. There was no operative mortality, although a patient died in the hospital, a month after operation, from uremia which was the result of the extensive renal destruction induced by the disease. Twelve (70 per cent) of these 18 patients were females. The ages varied from 13 to 62 years, the average being 43 years. Bony changes consisting of cysts or decalcification were found in 12 (70.5 per cent) cases. In 6 cases stones and changes in the bones occurred together. The urine was normal in 35 per cent of the cases. Bilateral stones occurred in 36 per cent of the cases.

A careful reexamination of all the patients who had a stone in the urinary tract is being undertaken by Barney. Thirty-three patients have been examined, which included not only routine physical examination and urinalysis, but also study of the blood chemistry and roentgenologic examination. In 11 patients the values for the serum calcium and serum phosphorus indicated hyperparathyroidism. Further examination of these patients will be made with this in mind. In only 2 instances were bony changes found at roentgenologic examination.

Priestley [10] reviewed 500 cases of renal calculosis and obtained data on types of calculi encountered, types of operations performed and pathologic changes associated with renal calculi. Unilateral stones were present in 85.2 per cent of the cases and bilateral stones in 14.8 per cent. There was about an equal division between multiple (55 per cent) and single (45 per cent) stones. In 10.4 per cent of the cases, calculus of the ureter was associated with nephrolithiasis. Treatment for these calculi varies, depending on the size of the ureteral stone, its situation in the ureter, the amount of infection present and the degree of ureteral dilatation.

Of these 500 patients, 8.6 per cent were operated on for recurrent calculi. The incidence of recurrence of renal calculi following their surgical removal has been variously estimated at from 8 to 40 per cent. Judd and Scholl found a recurrence in 10.4 per cent of 1,024 cases.

Of the various surgical procedures used in these cases, pelviolithotomy was performed in 44.6 per cent of the series; nephrolithotomy, in only 3 per cent. In recent years, pelviolithotomy has supplanted

10. Priestley, J. T.: Surgical Aspects of Renal Calculi, Proc. Staff Meet., Mayo Clin. 9:486 (Aug. 15) 1934.

nephrolithotomy as the operation of choice for removing renal calculi. The former procedure is safe, is easily performed, and is followed by excellent end-results. Nephrostomy was performed in 17.4 per cent of these cases. Priestley expressed the opinion that the more widespread use of nephrostomy, as advocated by Cabot, has done more than anything else in aiding to rehabilitate kidneys which previously would have been considered irreparably injured. Multiple operative procedures were carried out in 26.2 per cent of the cases. In this group are the more complicated cases, which include partial resection of the kidney, division of a horseshoe kidney, associated ureterolithotomy, combined pelvionephrolithotomy and nephrostomy. Nephrectomy was necessary in 26.2 per cent of cases.

Unilateral stones were removed in 95 per cent of cases, and bilateral, at a single admission, in 5 per cent. Operations may involve the kidney and ureter on the same side with less risk than when both sides of the urinary tract are involved. In general, it seems desirable to remove large branched bilateral renal calculi, because otherwise they usually lead to progressive renal injury and may demand emergency surgical treatment later. The entire mortality in the 500 cases of renal calculus was 2.3 per cent.

Various pathologic changes were found associated with renal calculi. Congenital anomalies were noted occasionally (5 per cent) and consisted of anomalous renal vessels, duplicated renal pelves, fused kidneys and ectopic kidneys. Generally, these conditions did not appear to be instrumental in the formation of calculi, unless the anomaly caused obstruction. Hydronephrosis, either moderate or marked, occurred in 61 per cent of cases. Although some hydronephrotic sacs were sterile, as in the case of a "primary stone," the renal pelvis frequently exhibited moderate inflammatory changes. In cases of pyonephrosis (10.6 per cent) infection was severe, and the kidney often changed to a densely adherent, thick-walled sac, filled with pus. A subcapsular type of nephrectomy is employed frequently in these cases. Kidneys with reduced function were noted in some cases (19 per cent), and in others (7.8 per cent) there was no function.

Cumming [11] said that the problem of treatment of bilateral calculi of the kidney and ureter is involved to a degree which makes the application of regular principles of procedure to all cases entirely impossible. Patients who have stones on both sides of the urinary tract are often seriously ill when first examined; they are always potentially so, and

11. Cumming, R. E.: Treatment of Bilateral Renal and Ureteral Calculi, J. Urol. **32**:600 (Dec.) 1934.

caution should be exercised. The results of routine tests to determine function, the presence of infection and the relationship of these factors to potential recovery of the kidney are not always borne out while the patient is under treatment. Conservatism will give the greatest satisfaction and tends to provide a longer period of life and comfort for the patients.

Cumming reviewed the general opinions of urologists on the subject of bilateral calculi, adding his personal comments. He expressed the opinion that certain generally accepted principles of treatment are not basically sound in spite of their long usage. His beliefs are based on experience and the work of many colleagues who agreed with him in the principles which he adopted years ago and have been satisfied with their clinical results.

The results of treatment and the follow-up records in a series of 43 cases provide evidence in favor of the procedure which has been outlined by Cumming. However, each individual case should be considered on its own merits, proceeding with the idea of saving the patient's life by preserving as much renal tissue as possible. Acceptable treatment also includes a constant study of all factors influencing the cause of primary stones and recurrences, and attempts to apply preventive treatment. Accessory factors, such as focal infection and ineffectual drainage, must be recognized and handled properly.

De Illyes [12] said that cases of renal calculosis have increased enormously since the war, especially in countries where living conditions have been poor. His article is concerned only with the recurrent formation of stones in kidneys that had previously been subjected to operation.

It often is difficult to distinguish between true recurrent calculosis and pseudoformation of calculi, for even if every traceable stone has been removed, there may be other minute ones remaining that were hidden by larger stones in the roentgenogram. Again, small pieces may become detached at operation and remain anchored in spite of the utmost care. There also may be minute stones or a gritty substance which is not revealed by the roentgenogram and which escapes detection during the operation. Another cause may be found in the operative technic; otherwise, there would be no explanation of the fact that the statistics of some surgeons reveal a great number of recurrences while those of others do not. Such conditions are not to be considered as true recurrences. Following 510 operations of the conservative type (pyelotomy, ureterotomy), there were 49 recurrences, of which 42 (7 per cent) were true recurrences and 7 were pseudorecurrences; 5 of these followed nephrotomy, and 44 followed pyelotomy and ureterotomy.

12. de Illyes, Geza: Des calculs rénaux récidivants, J. d'urol. **38**:419 (Nov.) 1934.

In de Illyes' statistics the percentage of recurrences after pyelotomy is somewhat higher than that of recurrences after nephrotomy since he was forced in most cases to remove the stone through the pyelotomy wound, a method of stone removal which is less dangerous than nephrotomy, even when severe perinephritis is present. Drainage in such cases is established by continuous catheterization of the ureter or by transrenal drainage.

Stones may be so opaque at times as to show no shadow or only a very vague one in the roentgenogram. In a case in which the stone was later immersed in water and then photographed, hardly anything was visible. This stone was found to consist of pure urate. This explains how easily a stone may remain in the kidney if its situation cannot be established beforehand.

It is possible now to take a roentgenogram of an exposed kidney by placing under the organ a film in a specially constructed and sterilizable case. The rigidity of the case, however, prevents a photograph of the whole organ. Therefore, Illyes recommended that the film be wrapped in dark paper, then in sterilized tin-foil or in a thin rubber sheet. This flexible film-pack is then placed under the kidney and permits roentgenography of either the whole organ or only the desired parts. In case any hidden stones are revealed, the operation may then be continued. This means of control is of great service.

Other important points in prevention of a recurrence of stone formation are: 1. The arrest of hemorrhages. If this is not possible, transrenal drainage and subsequent irrigation are necessary. 2. During pyelotomy, the renal pelvis must be sufficiently uncovered, and the incision should be extended to the renal parenchyma. After pyelotomy, a few stitches are helpful, even in cases of infection, if an indwelling catheter has been inserted. Care must be taken that the sutures do not touch the cavity of the renal pelvis. Furthermore, the kidney must be fixed sufficiently high.

Three causes of true recurrence of calculi may be mentioned: infection, retention and diathesis.

Infection always has been known as a major cause. Lately, it has been demonstrated that a number of bacteria may precipitate the colloids from the urine, and that they then serve as a nucleus around which phosphates and carbonates build up stones. Among the infectious bacteria, the staphylococci play the largest rôle by decomposing the urine. Ammonia is formed and the urine is thus rendered alkaline; this in turn favors the formation of calculi.

Retention is the accumulation of urine in the pelvis of the kidney or in the calices. It is sometimes difficult to determine whether the stone causes the retention or whether retention caused the formation of the

calculus. The most serious cases are those in which branched coral stones distend the intrarenal part of the renal pelvis and the calices, for even after removal of the stone a cavity remains, and the rigid wall of this cavity can maintain retention and encourage recurrence. In such cases, nephrectomy is always indicated if the other kidney is unaffected or only slightly affected. Cases in which only one or two calices are enlarged by retention are more favorable for operation than those with enlargement of all the calices, and recurrence of stone is less likely if a kidney which is uncovered at operation is not fixed fairly high. Another preventive measure is the removal of parts of a dilated renal pelvis.

The third factor of recurrence consists in diathesis during certain periods of life. Judd, Parker and Morse, therefore, expressed the opinion that recurrence is the result of the fact that the end of such a period has not arrived. They advised against renewed operative measures before the end of this period. But since most such operations are urgent, it unfortunately is rarely possible to postpone them. Braasch and Foulds also supported the hypothesis that formation of stones will persist until chemical balance is again attained. Although different diets can be prescribed for patients suffering from stones that are caused by uric diathesis, oxalic diathesis or excessive excretion of phosphates, the cause of the diathesis and of the formation of calculi still remains obscure. Attempts at dissolving stones in the organism have been partly successful, as demonstrated in cases in which there are stones in the bladder, either primarily formed or recurring after prostatectomy. While there are no chemical means known as yet for dissolving or reducing stones, their recurrence may be discouraged by an appropriate diet and by employing means to dissolve uric acid.

Herman and Greene [13] expressed the opinion that anuria with acquired single kidney is rare and less fatal if properly treated than are other types of obstructive anuria. Calculous anuria seldom occurs after nephrectomy for conditions other than calculous pyonephrosis; it is rare if the remaining kidney is normal at the time of the original operation. It is prone to occur after nephrectomy has been performed in cases in which there is cystinuria. In the majority of cases the indwelling catheter should be employed to overcome the anuria in preparation for removal of the obstructive stone or stones. Certain small calculi of the ureter, especially if impacted in the lower part of the ureter, may be removed by cystoscopy. The primary purpose of operation is to establish free urinary drainage. This may be done by operation on

13. Herman, L., and Greene, L. B.: Calculous Anuria in Acquired Single Kidney, J. Urol. **32**:623 (Dec.) 1934.

the kidney or on the ureter, as circumstances dictate, but primary ureterolithotomy is especially indicated in cases in which there are large stones in the ureter. In cases in which the condition is serious and especially in those in which the patients have been operated on previously, nephrotomy, with or without removal of the obstructive stone or stones, is the method of choice. In the majority of cases, the obstruction can be removed without too much damage to the kidney.

Tumors.—Geschickter and Widenhorn [14] expressed the opinion that most renal tumors may be related to stages of development of the permanent kidney. In spite of the difficulty in demonstrating the remains of embryonic nephrogenic tissue in the more slowly growing malignant nephromas and in the nephrogenic zone of the opposite kidney, comparisons of the structures of Wilms' tumor, the benign and malignant cystadenomas and the more rapidly growing malignant nephromas of young adults indicate that all of these nephrogenic tumors have their origin in a similar mother substance. Judging from the microscopic studies, this tissue of origin is the renal blastema, a compact group of spindle cells which differentiate into small tubular structures, composed of oval epithelial-like cells. This type of primitive tissue or renal blastema predominates in Wilms' tumors of children, the spindle cells being more prominent than early tubule formation. Among the benign and malignant cystadenomas of young adults, spindle cells and small tubules composed of oval epithelial cells predominate in many of the growths, particularly those which have undergone malignant change. In the nephromas, which affect elderly patients, the blastemic elements are difficult to demonstrate in all but the more malignant and rapidly growing tumors, but do occur. In the three groups of tumors taken as a whole, not only does the shift from immature spindle to adult epithelial forms appear to represent the cycle of growth within the individual tumor, but the extent of maturity reached, as shown microscopically by scarcity or prevalence of large epithelial elements, can be correlated definitely with the age incidence of the tumor and its relative degree of malignancy. The fact that all of these neoplasms show a distinct tendency to make their appearance just beneath the capsule in the normal growth zone of the kidney and the fact that the cortical zone of renal tissue normally continues to grow until adult life relate all of the growths to a single type of developing tissue. Consequently, the present study seems to indicate that the variations in structure which have been regarded as making for separate types of tumor are the expression of the various rates of growth and the extent of differentia-

14. Geschickter, C. F., and Widenhorn, Hans: Nephrogenic Tumors, Am. J. Cancer **22**:620 (Nov.) 1934.

tion achieved by the individual form of tumor rather than an indication of origin from separate and distinct tissues.

Randall [15] said that the embryonic character of renal tumors in infancy and childhood permits one to expect a marked diminution in their size from adequate roentgenotherapy. Such irradiation cannot be expected to be completely curative, that is, to destroy completely all neoplastic cells. Recurrences after irradiation exhibit increased resistance to this form of therapy, and ultimately the new growth exceeds irradiative destruction, that is, becomes "fast" to any type of irradiation. The fact that the consultant surgeon does not see these lesions early, owing to the latency of the symptoms, renders their operative removal both hazardous and at times impossible. Preoperative irradiation not only decreases this operative hazard but, by the decrease in size, minimizes the additional danger of manipulative and traumatic spread of malignant cells. The choice of time for operation, after the completion of thorough irradiation, appears to be between the fourth and the sixth week. There is no detriment to prompt healing in operating at this interval after irradiation. Those applying the radiation have learned the importance of watching the leukocytic count during the course of treatment. In some patients a leukopenia develops which is considered an evidence of lowered resistance and, if marked, contraindicates further irradiation at that time. Preoperative irradiation should include the thorax and abdomen, in an effort to create an unfertile field for metastatic transplants that may be dislodged in the handling of the tumor at the time of extirpation. Three cases in which the patient was treated by this method are reported.

In the first case described, the patient was treated in 1928, and the optimal time for operation was unavoidably missed. Death occurred subsequently from metastasis. In the second case, although the lesion was explored and considered inoperable, it was nevertheless rendered operable by irradiation, and nephrectomy was later performed easily. The patient was cured, but two years after the operation death occurred as the result of bronchopneumonia. A most complete necropsy proved the absence of the neoplasm. The third patient was in excellent health nine months after the operation; the specimen failed to show the presence of true malignant cells, though the preoperative study left no doubt of the existence of the tumor and its rapid disappearance under irradiation. As a result of the experiences of the past, this could not be taken as a cure, any more than the casually taken microscopic sections from this specimen could be taken as an indication of the absence of isolated nests of malignant cells elsewhere in the specimen.

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15. Randall, Alexander: Advantages of Pre-Operative X-Ray in Kidney Tumor in Children, Ann. Surg. **100**:462 (Sept.) 1934.

Sinkoe, Fowler and Berger [16] reported a case of Wilms' tumor of the kidney, and cited certain facts which verify the findings of other clinical investigators. A diagnosis should be made as early as possible and proper therapy immediately instituted. Early operative intervention offers the best prognosis. If the tumor is found to encroach on adjacent vital structures, the outlook is not favorable, because of surgical shock and the frequency of recurrence. The curative value of roentgenotherapy and radium therapy is questionable when they are used alone; however, in conjunction with surgical treatment, they may be of considerable value.

Shupe [17] expressed the opinion that tumor of the pelvis of the kidney is rare when compared with neoplasm of the renal parenchyma. Such tumors comprise about 7 or 8 per cent of all tumors of the kidney and are classified into two main groups, the papillary and the solid growths. The papillary tumors may be benign or malignant. The sessile growths consist of the transitional cell carcinoma and the squamous cell carcinoma. The papillary tumors are the most numerous, occurring in about 75 per cent of the cases of tumor of the pelvis of the kidney. Among 337 cases collected by Joly, there were benign papillomas in 120 cases, papillary carcinomas in 138 cases, transitional cell carcinomas in 29 cases and squamous cell carcinomas in 50 cases. The papillomas, whether benign or malignant, usually are multiple, are extremely vascular and bleed readily. This type progresses by extension to the calices, ureter and bladder. The solid tumors grow and extend by invasion of the renal vein and perirenal tissues. They metastasize remotely to the lungs, liver and bones.

The symptoms are those of any tumor of the kidney, of hydronephrosis or of calculi. This fact, plus their rare occurrence, is why tumor of the renal plevis is seldom diagnosed before intervention. Hematuria occurs in about 90 per cent of all cases in which there are papillary tumors and in 50 per cent of cases in which there are nonpapillary growths of the kidney.

Albarran found 8 growths of the bladder in 25 cases in which there was a tumor of the renal pelvis. Paris found 5 tumors of the bladder in 37 cases in which there was a tumor of the kidney. Occasionally, a polyp will almost completely block the orifice of the ureter, leading to hydronephrosis and a rapid development of the growths in the pelvis and ureter. When a papilloma is seen protruding from the orifice of

16. Sinkoe, S. J.; Fowler, M. F., and Berger, Louis: Wilms' Tumor of the Kidney: Report of Case with a Review of the Literature, Am. J. Surg. **25**:163 (July) 1934.

17. Shupe, T. P.: Tumors of the Renal Pelvis: Report of Two Cases, Tr. Am. A. Genito-Urin. Surgeons **27**:161, 1934.

the ureter, regardless of whether or not the bladder is involved, a diagnosis of renal and ureteral tumor is justified.

A simple papilloma, because of its habit of forming transplants in the ureter and bladder, must be considered at all times as potentially malignant. The accepted operative procedure in these cases is nephrectomy and total ureterectomy. This is especially true if the diagnosis is established as a result of the presence of transplants in the bladder and ureter.

Helfer and Schor [18] said that pyelography is a highly valuable method for the diagnosis of palpable tumor of the kidney. In the diagnosis of tumor of the kidney, repeated use of the pyelogram is an important aid in verifying characteristic changes in the form of the renal pelvis and in the position of the ureters. A tumor of the kidney may at times run its course without clinical symptoms. Therefore, whenever a mass is found in either side of the abdomen, it is necessary to determine by pyelography whether or not it is a tumor of the kidney. In cases of immovable tumor of the abdomen without symptoms from the bladder, it is at times difficult to determine whether or not the kidney is involved in the tumor mass. In cases of movable tumor, one is able, by means of pyelography, to decide definitely that the kidney is or is not involved in the mass. In cases in which the differential diagnosis of a tumor in the lower part of the abdomen presents difficulties, roentgenography of the intestine after the injection of an opaque medium is of great value.

Trauma.—Redi [19] said that the medical profession is divided into three groups with reference to the type of treatment to be applied following trauma of the kidney: out-and-out interventionists, moderate interventionists and out-and-out abstentionists. This diversity of opinion is caused in part by an error of interpretation, that is, by uncertainty as to the exact significance of the symptoms. It is a fact that there is no exact relation between the extent of the anatomicopathologic lesions in a given case and the general condition of the patient, and that the symptoms do not always give the key to the anatomic lesions and their later course of evolution. In all cases of renal trauma, the ascending and descending pyelograms, combined with the findings of functional tests, in their ensemble, give a clear picture of the type and extent of the lesion. Pyelography is not dangerous in cases in which the kidney has been injured, if carried out with complete asepsis; Redi has never encountered any complications from its use. With all the modern means of examination, it is possible to diagnose with approximate certainty

18. Helfer, P. I., and Schor, M. I.: Die Bedeutung der Pyelographie für die Differentialdiagnose der Bauchgeschwülste, Ztschr. f. urol. Chir. **39**:322, 1934.

19. Redi, R.: Les lésions traumatiques du rein et leur traitement, J. d'urol. **38**:231 (Sept.) 1934.

(1) whether a rupture is limited to the parenchyma of the kidney, (2) whether it includes the renal plevis, and (3) whether it involves the capsule as well as all the other parts of the organ.

Intervention does not necessarily mean nephrectomy. It may mean the reconstruction of the kidney. Severi recently undertook experiments with rabbits, in which he traumatized in all possible ways the kidney on one side, to demonstrate what functional value would remain after the animals had recovered. In these experiments, however, the capsule and the pedicle never were deliberately injured. The animals always survived the injury; the wounded kidney was replaced in its bed and sutured in the various planes. From fifteen to ninety days later, the kidney of the other side was removed. Function in the damaged kidney was always demonstrated from the earliest days after operation. The course of recovery could be divided into three states: (1) hemorrhagic infiltration, (2) signs of resorption and (3) evidence of cicatricial sclerosis.

An interesting and novel observation was that lesions of the renal parenchyma are most severe at the junction of the cortex and medulla; here, they appeared at first as lacunae filled with blood, and at a later time, as pseudocysts. A second interesting fact was that in the medullary portion of the kidney the lines of rupture all followed the direction of the straight tubules, and were in a great part the result of dissociation of these. Thus, the tubules themselves were left intact for the most part and none had suffered irreparable injury. Consequently, function was not interrupted even in the days immediately following the traumatism. These results encourage the surgeon to go ahead with his efforts to reconstruct the injured organ, and they indicate that even a severely traumatized kidney may be expected to hold its own and to regain full function. Five illustrations or cases are outlined which demonstrate the justification for a waiting course. On the basis of these, and as a result of the experiments referred to, it may, therefore, safely be said that, unless the pyelogram shows that the kidney has been completely destroyed, or that it has been detached from its pedicle, the indication exists for partial or multiple resection of the organ, after a preliminary partial decapsulation and resection of the margin of the wound. The use of tampons is not advised, as it may lead to fistulas, but the placing of a Mikulicz drain is imperative. Complications, such as infection, irreducible hematuria, hematonephrosis, true traumatic hydronephrosis, rupture of the peritoneum, infarct of the kidney or rupture of the pedicle, may necessitate nephrectomy in such cases. The surgeon should act quickly, according to the indications. This is also true in cases in which there is perforation of the peritoneum, crushing

on the kidney or detachment of the pedicle. In these cases, operation should be carried out promptly. The operation should be conservative if possible, but radical if necessary.

Partial Resection.—Kretschmer [20] said that whether solitary kidney is congenital in origin or the result of a previous nephrectomy, the problem of treating it when it becomes the seat of a serious lesion is the same. Among the lesions in a solitary kidney in which resection is indicated are a circumscribed collection of stones, especially with infection; the presence of a stone in a calyx, with dilatation and with a stricture of the neck of the calyx; hydronephrosis with destruction of parenchyma, and encysted calculi with formation of an abscess that leads to destruction of parenchyma. The operation is also indicated in cases of bilateral stone, in which one pole of the kidney is diseased; in cases in which there exists a circumscribed stone with formation of pus, and in partial hydronephrosis of the upper or lower pole, with the formation of stone. In cases of solitary cyst of the kidney, resection is at present recognized as the operation of choice, and usually is simple and not difficult to perform. The employment of this procedure is desirable in cases of double kidney with double pelvis in which half of the kidney reveals the presence of hydronephrosis, severe infection or stone, as well as in certain cases of metastatic infection of the kidney, that is, carbuncle of the kidney, and in cases in which there is poor function of the opposite kidney.

Hemorrhage was not a source of difficulty in resection of the kidney in the series of cases reported by Kretschmer, either at the time of operation or subsequently. In the cases of double kidney, it was a relatively simple procedure to isolate the vascular supply to the diseased half and to ligate the vessels before the resection was done. In 10 cases in which resection of normally formed kidneys was done, the bleeding was readily controlled with sutures. In none of these cases was the bleeding marked. In a case in which there was slight oozing, a piece of fat was transplanted. Careful suturing usually will prevent the occurrence of a postoperative fistula. When one of the calices has been opened, care should be taken in its closure with suture. The determination of the line of resection usually is simple. In cases of double kidney, a line of demarcation between the normal half and the pathologic half is readily discernible in most cases, although in a rare instance this may be absent or poorly defined. In the cases of solitary cyst, as

20. Kretschmer, H. L.: Resection of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **27**:249, 1934.

a rule, little difficulty is experienced in finding a line of cleavage between the cyst and the kidney.

Perirenal Hemorrhage.—By "spontaneous circumrenal hematoma" is meant a condition of extensive extravasation of blood into the renal bed and surrounding tissues which is unassociated with trauma. Despite the variety of causes, such hemorrhages present a fairly uniform clinical picture, so that they may be considered as representing a clinical entity. Heritage [21] reports 3 cases and reviews the 170 cases which have been reported in the literature. Etiologically, the cases fall into three groups:

1. Those cases in which the condition is caused by definite disease of the kidney or of its blood vessels. This group, which forms 58 per cent of the entire series of cases, includes neoplasms and inflammations of the kidney, aneurysms of the renal artery and arteriosclerosis. Compression, obstruction and thrombosis of the renal veins, with the resultant hemorrhagic infarction of the kidney, also are a common cause.

2. Those cases in which the condition is caused by extrarenal diseases. This group includes 22 per cent of the cases and is composed chiefly of instances of adrenal tumor, perinephritis, blood dyscrasia and nonrenal aneurysm. In these cases, the pressure of the hematoma on the renal vein produces a vicious circle and bleeding from the hemorrhagic infarction.

3. Those cases in which the cause of the condition is obscure. This group forms 20 per cent of the cases. In this group, although the cause is unknown, the kidney seems to be the most likely source of the bleeding. This is supported by the frequent finding of blood and albumin in the urine and by the fact that recovery follows nephrectomy.

In none of these cases was an acutal bleeding point seen at operation, and on microscopic section the kidneys did not reveal any change except venous congestion. In 8 cases in which the origin was unexplained, and in which nephrectomy had been performed, all of the patients survived, while in 19 cases in which drainage alone was done, only 10 patients survived. In some cases, extrarenal hemorrhage ceases spontaneously; the hematoma becomes encapsulated and forms a pararenal hemorrhagic cyst.

The classic symptoms are abdominal pain, shock, signs of internal hemorrhage and a tumor in the loin which increases in size. The diagnosis may be missed because these signs suggest an acute intra-abdominal catastrophe, such as a perforated ulcer.

In the 155 cases in which the condition was treated surgically, the various procedures resulted as follows: Expectant treatment only,

21. Heritage, Kenneth: Spontaneous Circumrenal Hematoma, Proc. Roy. Soc. Med. **27**:1105 (June) 1934.

which was employed in 50 cases, resulted in 50 deaths; drainage only, which was employed in 51 cases, resulted in 23 deaths; nephrectomy plus drainage, which was employed in 54 cases, resulted in 14 deaths.

When a grossly diseased kidney is the source of bleeding, nephrectomy should be carried out. In cases in which the hematoma is of extrarenal origin, the prognosis is poor unless a blood vessel can be caught and ligated. In the third group, those cases in which no cause can be found, the best results follow nephrectomy.

TESTIS

Tumor.—Herger and Thibaudeau [22] reported cases of tumor of the testis from the State Institute for the Study of Malignant Disease at Buffalo. Their records show 63 cases in which tumor of the testis was treated at the institute. Of these, 56 were studied histologically. Fifty-five of these tumors are classed with the teratomas, while the other shows the histologic picture of a fibrosarcoma. The entire group of teratoma of the testis shows the average age of incidence to be 33 years. Eighty per cent of the patients were between the ages of 20 and 40 years, while 95 per cent were between 20 and 50 years of age. They noted that cases in which the tumor occurred in the second and third decades presented a much more unfavorable prognosis than did those in which the tumor occurred in the fourth and fifth decades. Their records showed that of 24 patients who were admitted before or at the age of 30 years, only 2 survived for three years, while 11 of the 30 patients who were between 31 and 50 years of age are still living after a three year period. For purposes of their study, Herger and Thibaudeau divided the malignant teratomas of the testis into five groups. In the first, malignant teratoma with adult features, they have included the tumors presenting definite adult structures, cartilage, fat cells, adult squamous epithelium, smooth muscle fibers and so forth. Even the malignant portions of these teratomas have presented evidence of adult type and have revealed their source from more or less differentiated cells. The records of the institute show 7 instances of this type of tumor.

The second group, embryonal carcinoma (seminoma), are tumors made up of large, round or polyhedral cells which have vesicular hyperchromatic nuclei characteristically growing in large sheets or alveoli. Twenty of the tumors belonged in this histologic group. Only 1 of the patients who had tumors of this type presented himself without demonstrable metastasis; 1 is alive and well ten years after irradiation and orchidectomy; 2, who have undergone treatment for less than one

22. Herger, C. C., and Thibaudeau, A. A.: Teratoma of Testis, Am. J. Cancer **22**:525 (Nov.) 1934.

year, have persistent metastasis; 1 has not been traced, and the other 15 are dead. Twelve of the deceased survived for less than one year; the remaining 3 lived fifteen months, two years, and four years and nine months, respectively. In this group, treatment usually caused some recession of the metastasis, but rarely was complete disappearance noted. Apparently, the treatment was effective only in producing a temporary restraint of growth of the tumor; increased activity or new metastasis ultimately appeared which did not respond to treatment.

In the third group, embryonal carcinoma with lymphoid stroma, the presence of lymphocytes in the stroma in varying numbers is characteristic. After histologic examination, 17 of the tumors were classified in this group. In these cases, the patients presented themselves for treatment at the institute. Of these, 9 did not reveal demonstrable metastasis, while 8 revealed definite metastasis or local recurrences. The 9 patients who did not reveal metastasis were all treated with roentgen rays of high voltage and orchidectomy, and in none of these cases have recurrences or metastasis developed. All of these patients are alive and well. Of the 8 patients who revealed metastasis at the time of their admission, 3 are dead after living for four years, two and one-half years, and ten months, respectively. The remaining 5 are alive and apparently well, 1 for ten years, 1 for three years, 1 for one year, and 2 recent patients, still undergoing treatment, for less than one year.

Embryonal adenocarcinoma, which comprises the fourth group, presents definite characteristics. The typical picture is that of alveoli which are lined with large cuboidal or low columnar cells with hyperchromatic nuclei. The growth is often papillary, though in some areas it may assume a more solid form, with smaller cells and less differentiation. Herger and Thibaudeau have studied 11 cases of this type of tumor of the testis. Metastasis or local recurrence was present in all the patients when first seen. Only 1 patient who had this type of tumor is still living. Treatment of this type of tumor was of no avail, and the patients, all but 1, succumbed in from two to eight months. In this particular group of tumors, the clinical course was uniformly and rapidly fatal.

Chorionepithelioma, which comprises the last group, is identical in histology with the same tumor in the uterus. Characteristically, it presents the usual syncytial cells, which often resemble squamous epithelial cells, some multinucleated, in more or less disorderly arrangement. In the majority of cases, the usual treatment of simple orchidectomy followed by irradiation of the lymph-bearing areas was carried out. Usually the patients were referred and had undergone operation elsewhere, before admission to the institute. Often several months had elapsed between operation and irradiation. It is most desirable that patients

with this type of tumor be referred for treatment immediately after operation, as otherwise valuable time is lost and opportunity is provided for a spread and increase in the amount of tumor tissue. Irradiation has consisted of high voltage roentgen rays (200 kilovolts) with an effective wavelength of 0.16 angstrom. For abdominal and thoracic areas, a total of approximately 2,500 roentgens, divided between two fields, anterior and posterior, is administered in a period of eight days. This is repeated in from six to eight weeks. Some patients have been treated with the 4 Gm. radium element pack. At from 10 to 15 cm. skin distance, erythema doses are applied to anterior and posterior fields. Both of these procedures apparently have resulted in complete regression of large mediastinal metastases. Large abdominal masses also vanish rapidly in some cases. Of 36 patients available for three year statistics, 13 (36 per cent) survived three years or longer. Of 21 patients available for five year statistics, 7 (33.3 per cent) survived five years or longer. The authors stated that their limited experience with the quantitative Aschheim-Zondek reaction convinces them of its value as a diagnostic procedure and as an aid in the conduct of treatment.

Hinman and Powell [23] expressed the opinion that the pituitary body, pregnancy and embryonal tumors are known causes of the appearance in the urine of gonad-stimulating hormones. The stimulation of the growth of the gonads and genitals of infantile animals varies with the origin of the hormone producing it, the amount present in the urine and the animal used for the injections. The microscopic ripening of graafian follicles is more easily studied with mice than with rats. The gross enlargement of the uterine horns is more definite in rats than in mice. At the age of 20 or 21 days the ovary of the rat normally may show open follicles. The hydrocele fluid in the presence of tumor of the testis contains more of the hormone than does the urine of the patient.

The majority of tumors of the testis are embryonal, and the urine of patients who have these tumors contains a substance which produces gross enlargement of the uterine horns or microscopic ripening of the ovarian follicles when injected into infantile female mice and rats. The presence of such a gonadotropic hormone in the urine of a patient who has a tumor of the testis is presumptive evidence of malignancy of the tumor, and its absence is strong, but not definite, evidence against malignancy. The effect of irradiation on the amount of hormone in the urine, as determined by quantitative methods before and after the

23. Hinman, Frank, and Powell, T. O.: The Gonadotropic Hormone in the Urine of Men with Tumor of the Testis, Tr. Am. A. Genito-Urin. Surgeons **27:** 359, 1934.

irradiation, gives a good indication of the radiosensitivity of the tumor and may be used as a therapeutic test, in conjunction with the clinical effect on metastasis, when present. The effect of irradiation as a therapeutic test must be interpreted in conjunction with the histologic structure of the tumor, the clinical absence of metastasis, or the character of the metastasis when present, and the physical condition of the patient. The hormonal test permits a more accurate prognosis and a better control of therapy than has been possible heretofore, and may be of value in the classification of tumors the nature of which is in doubt from histologic study alone.

Hinman [24] said that the first step in the treatment of tumors of the testis is early and definite diagnosis. The hormonal test seems to indicate with accuracy the presence or absence of a malignant growth of the testis, but it is not entirely specific. A positive result may be caused by the pituitary hormone, which is increased because of gonadal deficiency, such as occurs with bilateral castration, or cyclically among normal men; it also may be caused by an embryonal tumor elsewhere than in the testis. A negative result is good, though not positive, evidence that there is not a malignant tumor of the testis. A pure seminoma may not cause the excretion of the hormone. The diagnosis can be determined definitely by histologic examination after castration. A study of histologic structure is necessary to prognosis and the control of treatment. Until recently, all tumors of the testis were regarded clinically as similar, always malignant, and as having the same route of metastasis. Experience with radiation has demonstrated a marked variability in the sensitivity of these various growths, and the newly applied hormonal test shows a difference in the amount of hormone excreted in the urine of patients who have different types of malignant tumors.

The second step in the treatment of tumors of the testis is the determination of whether or not there is metastasis by clinical examination and the biologic test. Patients who have no metastasis fail to excrete the hormone within two weeks after castration. When the hormone persists, though reduced in quantity, metastasis is probably present, even though it cannot be demonstrated clinically.

The third consideration in the treatment of a tumor of the testis is radiosensitivity. This can be predicted by past experience with similar tumors and can be tested clinically by noting the effect of irradiation on metastasis when present and on the amount of hormone in the urine. The determination of this sensitivity may be called the therapeutic test of irradiation.

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24. Hinman, Frank: The Prognosis and Treatment of Tumors of the Testis, Tr. Am. A. Genito-Urin. Surgeons **27**:379, 1934.

On the basis of diagnosis, metastasis and radiosensitivity, patients may be divided, for purposes of treatment and prognosis, into two groups: Group 1 includes those patients without clinical evidence of metastasis who are in good physical condition; these can be subdivided by the result of a hormonal test, two weeks after castration, into a negative subgroup and a positive subgroup. Group 2 contains patients who have clinical evidence of metastasis. Castration may be indicated for local relief, but mainly for diagnosis. Experience has demonstrated that these patients have tumors which are inoperable, and that irradiation is the only curative treatment. The prognosis depends on the extent and rapidity of growth of the metastases and on the general physical condition of the patient as well as on the type of tumor and its radiosensitivity.

Of 25 patients in group 1, 14 were subjected to radical operation, 9 for a tumor on the right side, and 5 for a tumor on the left side. Ten of these patients are living, all with a favorable prognosis. Four are dead. Seven disclosed metastases in the lymph nodes which were removed at operation. Four of these are living fourteen years, four years and ten months, one year and one month, and three months, respectively, after the operation. Three are dead. Seven had lymph nodes which did not show metastases when they were removed. In 2 of these cases, there was an unusual degree of endothelial hyperplasia; in one of the latter cases the patient is living and well six years and one month later, and in the other case the patient is dead. The 5 others are now living eight years and nine months, two years and eight months, one year and four months, one year, and one year, respectively, after the operation. Of the 11 patients who did not reveal metastases and who were treated by castration and roentgenotherapy, 8 are living; 1 for two years, with a favorable prognosis; 4 with only a fair prognosis because the hormonal tests are positive, and 3 with a definitely poor prognosis. Of the 4 patients with a fair prognosis, 1 lived seven years before metastasis occurred, but the amount of the hormone in the urine is increasing in spite of roentgenotherapy; 1 has lived seven years since castration, and, although metastasis is not evident clinically, the amount of the hormone in the urine is increasing. The other 2 who have a fair prognosis have lived one and three years, respectively, without clinical evidence of a metastasis, but with positive hormonal tests.

Of the 29 patients in group 2, only 10 are alive; 4 have a fair prognosis and are living five years, one and one-half years, six months, and a few months, respectively, after the operation, but all have positive hormonal tests, and 6 have a poor prognosis (radioresistant).

MacKenzie [25] reported 2 cases of malignant growth in the undescended testis, but expressed the opinion that there is not much danger of malignant changes in undescended testes, whether inguinal or abdominal. There is no definite proof that undescended testes are predisposed to malignant changes. In a review of the literature, various reports contain assertions to the effect that tumors occur from thirty to three hundred times as frequently in the undescended as in the normally placed gonad. There also are differences of opinion regarding the relative frequency of malignant conditions in testes which are situated in the inguinal region or in the abdominal cavity. The following are some of the reports regarding malignant growths in undescended testes: Deane reported that 13.5 per cent of all tumors of the testis were found in undescended organs. Hinman reviewed 649 cases of carcinoma of the gonads and found that 12.2 per cent involved undescended testes. Rubaschow reviewed the cases of this condition which had been reported by 21 observers, and found that in 11 per cent of the whole group tumors were present. This figure is a rather high one. Eccles reported 859 cases of undescended testes without finding a malignant growth in any of them. Coley did not find a malignant tumor in 1,357 cases of undescended testes. Kocher found only 1 malignant tumor in 1,000 cases. Hinman expressed the opinion that 1 instance of malignant tumor of an abdominal testis is found in every 60,000 cases of undescended testes.

MacKenzie's method of treatment of tumor of the testis, whether undescended or normally placed, has been changed in the past few years. A course of treatment with roentgen rays of high voltage is first given. This is followed by orchidectomy and several courses of roentgenotherapy extending over a long period. Patients report every two or three months for observation. Since this new method has been used, the results have been more satisfactory; even those patients who disclosed metastases when they first sought treatment seem to have improved. In a small number of cases in which there were metastases in the thorax and retroperitoneal glands, the masses have entirely disappeared or have been reduced considerably in size after the course of treatment with roentgen rays of high voltage. MacKenzie expressed the opinion that no undescended testis per se should be subjected to orchidectomy.

Robertson and Gilbert [26] summarized 7 cases of tuberculosis and carcinoma of the testis from the literature and reported a case of their

25. MacKenzie, D. W.: Malignant Growths in the Undescended Testis: Review of the Literature and Report of Two Cases, Tr. Am. A. Genito-Urin. Surgeons **27**:399, 1934.

26. Robertson, J. P., and Gilbert, J. B.: Coexistent Cancer and Tuberculosis of the Testicle: Case Report and Complete Review of the Literature, J. Urol. **32**:291 (Sept.) 1934.

own. The youngest patient was 28 years of age, while the oldest was 53 years of age; the average age of these patients was 38.3 years. The right side was involved in 4 cases, the left in 3 cases, and in one instance an undescended testis on the right side was involved. The duration of the known presence of a tumor varied from six weeks to four years. In 3 instances, tuberculosis was present elsewhere in the body: in the bones (rib) in 1 case, and in the lungs in 2 cases. Three patients previously had had gonorrhea. Carcinoma was associated with the tuberculosis in 6 instances, and seminoma was associated with the tuberculosis in 2. A survey of the coincidence of tuberculosis of the epididymis and malignant tumors of the testis is recorded, as well as the incidence of tumors of the testis which were associated with pulmonary tuberculosis. It is emphasized that diagnosis in the atypical case often is difficult; mistakes are costly, and surgical exploration or irradiation should be employed in cases in which the nature of the tumor is in doubt. The routine use of the quantitative Aschheim-Zondek reaction is advocated.

Castration.—McCullagh and Renshaw [27] subjected 12 postpubertal castrates to careful clinical and laboratory studies to increase familiarity with the diagnostic evidence of hypogonadism of man. Complete castration produced nervous and vasomotor disorders as early as the third day after operation. This nervous excitability was in some cases associated with a tendency to psychoneurosis, emotional instability and restlessness —a sensation not unlike that resulting from a mild overdose of thyroid extract. Hot flashes occurred as many as four or five times daily for a period of several years, and tended gradually to decrease in number and severity. All of the patients had diminished sexual potency and libido. Sexual impotence was not a distressing symptom in the absence of sexual desire, but in 3 cases in which there was a partial retention of libido even partial impotence became a distressing symptom. After the acute nervousness had subsided, the patients tended to display a quiet, phlegmatic temperament. Atrophy of the prostate was a constant and striking feature in all of these cases. The size of the prostate glands varied from a half to a fifth of normal. Vigorous and repeated massage failed to produce any prostatic secretion in 8 of the cases. Atrophy of the penis was recorded in only 5 cases. Hirsuties was definitely reduced, except for the scalp, and was of a female distribution. Eight patients showed abnormal accumulations of fat, chiefly about the abdomen and breasts. There were no gross skeletal changes. The skin became somewhat atrophic and was thin, slightly dry and finely wrinkled in 11 cases. The teeth, finger-nails, thyroid gland and pituitary body did not reveal any changes. Eight of 9 patients who were subjected to

27. McCullagh, E. P., and Renshaw, J. F.: Effects of Castration in the Adult Male, J. A. M. A. **103**:1140 (Oct. 13) 1934.

the Friedman test revealed definite evidence of increased gonad-stimulating principle in the urine, as compared to normal men subjected to similar tests. The basal metabolism of these patients was low. Serum calcium estimations were within normal limits in 11 cases.

The testis hormone, which is prepared from urine, when available for adequate dosage, produced considerable improvement in the subjective symptoms of hypogonadism. It is too early to evaluate accurately the benefits of this type of treatment.

EPIDIDYMIS

Filariasis.—Ferrer [28] said that filariasis of the spermatic cord and filariasis of the epididymis are two different lesions, with separate symptoms. A correct diagnosis of either condition can be made with a definite degree of certainty before determining the operative procedure to be used. Microfilariae may persist in the superficial circulation for a number of years even after radical surgical intervention, provided that a secondary infection with adult organisms has taken place later, or that there is another focus producing the periodic outpouring of microfilariae.

The principal differences between filariasis of the spermatic cord and that of the epididymis are as follows: In filariasis of the cord there is a history of intermittent hydroceles with a final permanent hydrocele. This condition is characterized by fibrosis, anterior nodules and typical sequelae of inflammatory reaction of the anterior portion of the cord. The diagnosis is confirmed by the finding of the living or dead parasite. In filariasis of the epididymis, there are attacks of colic, with constitutional symptoms, and there never is a hydrocele during or after the attack, unless it may be caused by other factors. The involvement is circumscribed to the globus major, and the adult organism should be found in sections of the specimens which are removed to confirm the preoperative diagnosis. Only radical surgical intervention will cure the disease. It should be remembered, however, that the condition may be bilateral, and that the testis should be preserved intact for internal, and possibly for external, secretory function.

SPERMATIC CORD

Tumors.—Fresnais and Mouchet [29] reported a case of malignant tumor of the spermatic cord, which recently was observed in Marion's clinic. The growth, which began 1 cm. above the testis and measured

28. Ferrer, J. C.: Filariasis of the Spermatic Cord and of the Epididymis, J. Urol. **32**:710 (Dec.) 1934.

29. Fresnais, Jean, and Mouchet, Alain: Un cas de tumeur maligne du cordon spermatique, J. d'urol. **38**:259 (Sept.) 1934.

11 cm. in length, involved almost all the elements of the spermatic cord, which could not be recognized or dissociated; the vas, however, remained intact, and the testis, epididymis and tunica vaginalis were all normal. The exact nature of the tumor could not be determined, but in view of the polymorphism of its cells and the presence of numerous eosinophils, a diagnosis of lymphogranulomatosis appears to deserve consideration, although epithelioma and sarcoma could not be excluded. A search of the literature revealed only 44 cases of malignant tumor of the spermatic cord, 22 of which were analyzed by Patel and Chalier in 1909, while the other 22 have been reported by various authors since that time. In 38 of the cases, the tumors were sarcomas, and among these the fibroblastic sarcomas were the most characteristic. Sarcomas of the spermatic cord, however, rarely present a uniform appearance. Celso and Karo were both struck by the variety of the cellular elements in the tumor which was found in their case, and decided to call it by the inexact name of "poly-morphous-celled sarcoma, myxo-lipo-sarcoma, and myxo-chondro-sarcoma." The most individualized group is that of lymphosarcoma, the round cell sarcoma of the older authors, which is characterized by autonomous and undifferentiated proliferation of the lymphoid cells, but the only clearcut case of this type of tumor was that reported by Allende and Gonzalez [30] in 1930. All types of sarcoma may affect the spermatic cord, and the tumor most frequently is one of the mixed type.[31] The conspicuousness of certain tissues, for example, the lipoid tissue, seems to point to a tumor which originally was benign but which has undergone malignant degeneration. However, the line between epithelioma and sarcoma is not easy to draw, and the case reported here is particularly open to this indefiniteness. No satisfactory classification of tumors of the spermatic cord has ever been made. The tumors generally appear between the ages of 40 and 70 years. The site of the tumor usually is on the left side of the cord; it may be in either the inguinal or the scrotal portion of the cord. The growth develops insidiously; its evolution may require years or only months. The prognosis should be reserved. In the case reported, the tumor has not reappeared in the five months that have elapsed since its removal. Treatment consists in the extirpation of the tumor and the testicle en bloc after high ligation of the cord; such extirpation is generally easy, owing to the absence of adhesions. Postoperative radiotherapy is indicated.

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30. Allende, J. M., and Gonzalez, R.: Tumor del cordón espermático, Bol. y trab. de la Soc. de cir. de Buenos Aires **14**:671 (Oct. 1) 1930.

31. Hinman, Frank, and Gibson, T. E.: Tumors of the Epididymis, Spermatic Cord and Testicular Tunics, Arch. Surg. **8**:100 (Jan.) 1924.

Varicocele.—Do Amaral [32] discussed the merits of a new method of surgical treament of varicocele. After making the usual type of incision, as for inguinal hernia, the testis is exteriorized by making gentle traction on the cord, with the help of compression from below upward. Working from above downward, the vas deferens must be separated from the varicose veins by means of a grooved sound; at the lowermost part of the spermatic cord, this procedure can be done best with the aid of gauze compresses. The bundles of veins are separated from the vas, down to the testis. Then comes the most delicate part of the operation; this consists in the exposure and isolation of the varicose veins without rupturing any of the anastomoses. This is done from above downward, beginning at the uppermost part of the spermatic cord, where, instead of a confused agglomeration of innumerable interlacing veins, only two or three relatively large vessels are found, which constitute the termination of all the bundles of the pampiniform plexus. The tunica vaginalis is now open and inverted, and is held in place by two or three catgut stitches, no. 00, as in the treatment of hydrocele, but the stitches are so placed as to form a jacket over that part of the spermatic cord which remains outside of and below the aponeurosis of the external oblique muscle, to prevent venous stasis. The vas, with its artery and satellite veins, is then separated and placed under the internal oblique and transversalis muscles, which in their turn are sutured to Poupart's ligament with chromicized catgut or with silk; the testis is replaced in the scrotum, care being taken not to make any torsion of the cord. At this point comes the deviation from the usual procedure. Instead of extirpating the varicose veins, they are left lying extended over the internal oblique and transversalis muscles, and covered with the aponeurosis of the external oblique muscle, which hides and compresses them, as an elastic stocking does the veins of a leg. It was believed that the veins would be held in this position, owing to the adhesions which would form later. But when the method did not prove effective in this respect, the device of a small buttonhole in the aponeurosis of the external oblique was tried, and served very satisfactorily; the varicose veins were hooked out through this small opening in the form of a loop, by means of a retractor, after which a U-shaped stitch was placed in the middle of the buttonhole to prevent the veins from slipping down again into the scrotum. In restoring the external orifice of the inguinal canal, care must be taken to narrow it, leaving barely enough room for the spermatic cord to pass from the deep plane to the veins of the supra-aponeurotic plane. The results obtained with this buttonhole modification were highly satisfactory; all the objective and subjective

32. do Amaral, Zephirido: Traitement du varicocèle par une nouvelle méthode chirurgicale, J. d'urol. **38**:249 (Sept.) 1934.

symptoms disappeared, the integrity of the vessels, both arteries and veins, was conserved, reflux was corrected, and the bulging varicosities within the scrotum, which are so distracting to the patient's mind, disappeared. The procedure corrects orchidoptosis, and also can be used to correct a hernia or a hydrocele at the same time as the varicocele is corrected.

(To be concluded)

CORRECTION

In the article by Drs. L. J. Adelstein and George H. Patterson, entitled, "Surgical Treatment of Ependymal Glioma of the Spinal Cord," in the June issue (*Arch Surg.* **30**:997, 1935), figures 2 (page 1004) and 6 (page 1009), but not the legends, have been transposed.